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| (54) Title: INHIBITORS OF PICORNAVIRUS 3C PROTEASES AND METHODS FOR THEIR USE AND PREPARATION (57) Abstract Picomaviral 3C protease inhibitors, obtainable by chemical synthesis, inhibit or block the biological activity of picomaviral 3C proteases. These compounds, as well as pharmaceutical compositions that contain these compounds, are suitable for treating patients or hosts infected with one or more picomaviruses. Several novel methods and intermediates can be used to prepare the novel picomaviral 3C protease inhibitors of the present invention. | | |

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INHIBITORS OF PICORNAVIRUS 3C PROTEASES AND METHODS FOR THEIR USE AND PREPARATION

The invention pertains to the discovery and use of new compounds that inhibit the enzymatic activity of picornaviral 3C proteases, specifically rhinovirus proteases (RVPs), as well as retard viral growth in cell culture.

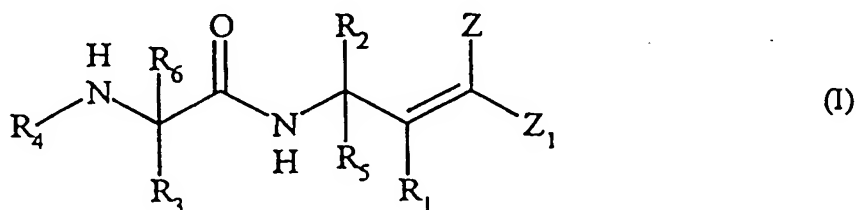
The picornaviruses are a family of tiny non-enveloped positive stranded RNA containing viruses that infect humans and other animals. These viruses include the human rhinoviruses, human polioviruses, human coxsackieviruses, human echoviruses, human and bovine enteroviruses, encephalomyocarditis viruses, menigovirus, foot and mouth viruses, hepatitis A virus and others. The human rhinoviruses are a major cause of the common cold. To date, there are no effective therapies to cure the common cold, only treatments that relieve the symptoms.

One strategy that may be useful to treat picornaviral infections is by inhibiting the proteolytic 3C enzymes. These enzymes are required for the natural maturation of the picornaviruses. They are responsible for the autocatalytic cleavage of the genomic, large polyprotein into the essential viral proteins. Members of the 3C protease family are cysteine proteases, where the sulfhydryl group most often cleaves the glutamine-glycine amide bond. In theory, inhibition of 3C proteases can block proteolytic cleavage of the polyprotein, which in turn can retard the maturation and replication of the viruses by interfering with viral particle production. Therefore, inhibiting the processing of this cysteine protease with selective, small molecules that are specifically recognized, may represent an important and useful approach to treat and cure viral infections of this nature and, in particular, the common cold.

SUMMARY OF THE INVENTION

The present invention is directed to compounds that function as picornaviral 3C protease inhibitors, particularly those that have antiviral activity. It is further directed to the preparation and use of such 3C protease inhibitors. The Inventors demonstrate that the compounds of the present invention bind to rhinovirus 3C proteases and preferably have antiviral cell culture activity. The enzymatic inhibition assays used reveal that these compounds can bind irreversibly, and the cell culture assays demonstrate that these compounds can possess antiviral activity.

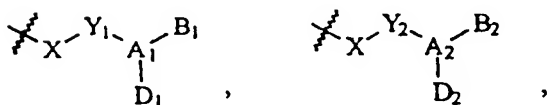
The present invention is directed to compounds of the formula (I):



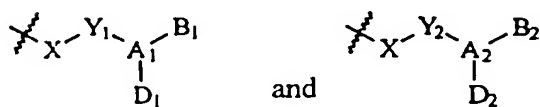
wherein

R₁ is H, F, an alkyl group, OH, SH, an O-alkyl group, or an S-alkyl group;

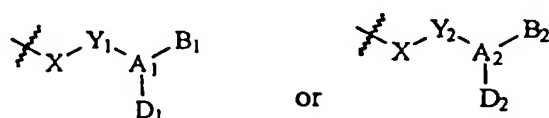
R₂ and R₃ are independently selected from H,



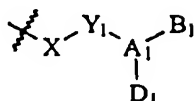
or an alkyl group, wherein said alkyl group is different from



with the proviso that at least one of R_2 or R_3 must be



and wherein, when R_2 or R_3 is



X is $=\text{CH}$ or $=\text{CF}$ and Y_1 is $=\text{CH}$ or $=\text{CF}$

or X and Y_1 together with Q' form a three-membered ring

in which Q' is $-\text{C}(\text{R}_{10})(\text{R}_{11})-$ or $-\text{O}-$, X is $-\text{CH}-$ or $-\text{CF}-$, and Y_1 is $-\text{CH}-$, $-\text{CF}-$, or $-\text{C}(\text{alkyl})-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{CHF}-$, or $-\text{S}-$,

and

Y_1 is $-\text{O}-$, $-\text{S}-$, $-\text{NR}_{12}-$, $-\text{C}(\text{R}_{13})(\text{R}_{14})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{CR}_{13}\text{R}_{14})-$

wherein R_{12} is H or alkyl, and R_{13} and R_{14} independently are H, F, or an alkyl group, or, together with the atoms to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

and A_1 is C, CH, CF, S, P, Se, N, NR_{15} , $S(O)$, $Se(O)$, $P-OR_{15}$, or $P-NR_{15}R_{16}$

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

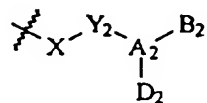
and D_1 is a moiety with a lone pair of electrons capable of forming a hydrogen bond;

and B_1 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$

wherein R_{17} , R_{18} , and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or, wherein any two of R_{17} , R_{18} , and R_{19} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group; and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N;

and wherein, when R_2 or R_5 is



X is =CH or =CF and Y_2 is =C, =CH or =CF,

or X and Y_2 together with Q' form a three-membered ring

in which Q' is -C(R_{10})(R_{11})- or -O-, X is -CH- or -CF-, and Y_2 is -CH-, -CF-, or -C(alkyl)-, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is -CH₂-, -CF₂-, -CHF-, or -S-,

and

Y_2 is -O-, -S-, -N(R'_{12})-, -C(R'_{13})(R'_{14})-, -C(O)-, -C(S)-, or -C(CR'₁₃R'₁₄)-

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, -OR'₁₃, -NR'₁₃R'₁₄, -C(O)-R'₁₃, -SO₂R'₁₃, or -C(S)R'₁₃, and R'_{13} and R'_{14} , independently are H, F, or an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

and wherein any combination of Y_2 , A_2 , B_2 , and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and A_2 is C, CH, CF, S, P, Se, N, NR₁₅, S(O), Se(O), P-OR₁₅, or P-NR₁₅R₁₆

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

and D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond;

and B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$

wherein R_{17} , R_{18} , and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or, wherein any two of R_{17} , R_{18} , and R_{19} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

R_3 and R_6 are independently H, F, or an alkyl group;

R_4 is H, OH, or a suitable organic moiety;

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21} , R_{22} , R_{23} , and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21} , R_{22} , R_{23} , and R_{24} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

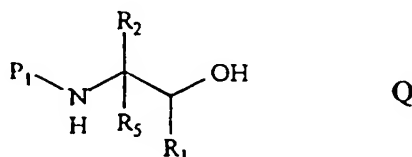
or Z_1 , as defined above, together with R_1 , as defined above, and the atoms to which Z_1 and R_1 are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z_1 , both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

and pharmaceutically acceptable prodrugs, salts, and solvates thereof;

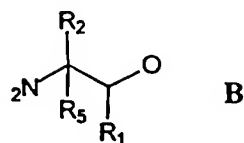
and wherein these compounds, pharmaceutically acceptable prodrugs, salts, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

The present invention is also directed to several methods of preparing compounds of formula (I), defined above. One method according to the invention involves converting a compound of formula Q



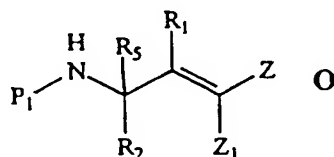
wherein R_1 , R_2 and R_5 are as defined above, and P_1 is a protective group, preferably benzyloxy carbonyl or t-butoxycarbonyl, or a salt or solvate thereof, to a compound of formula I, as defined above, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

Another method according to the invention involves converting a compound of the formula B:



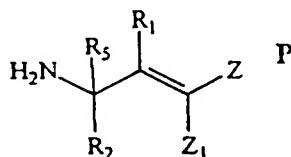
wherein R₁, R₂ and R₅ are as defined above, or a salt or solvate thereof, to a compound of formula I, as defined above, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

Another method according to the invention involves converting a compound of formula O:



wherein R₁, R₂, R₅, Z and Z₁ are as defined above and P₁ is a protective group, preferably benzyloxy carbonyl or t-butoxycarbonyl, or a salt or solvate thereof, to a compound of formula I, as defined above, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

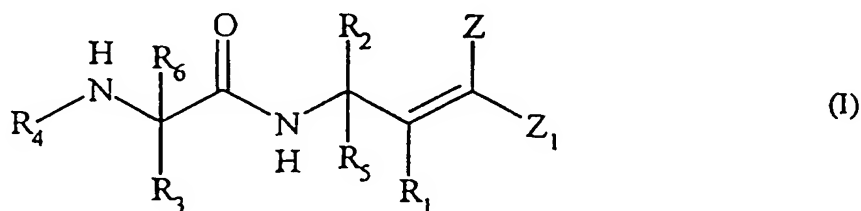
Another method according to the present invention involves converting a compound of formula P:



wherein R_1 , R_2 , R_3 , Z and Z_1 are as defined above, or a salt or solvate thereof, to a compound of formula I, as defined above, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

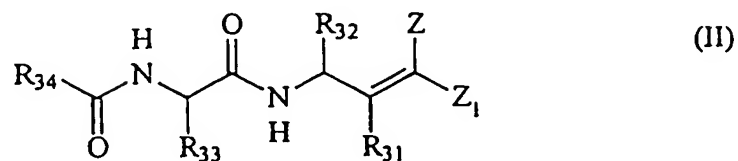
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the formula I



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , Z and Z_1 are as defined above, and to the pharmaceutically acceptable prodrugs, salts, and solvates thereof, where these compounds, pharmaceutically acceptable prodrugs, salts, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

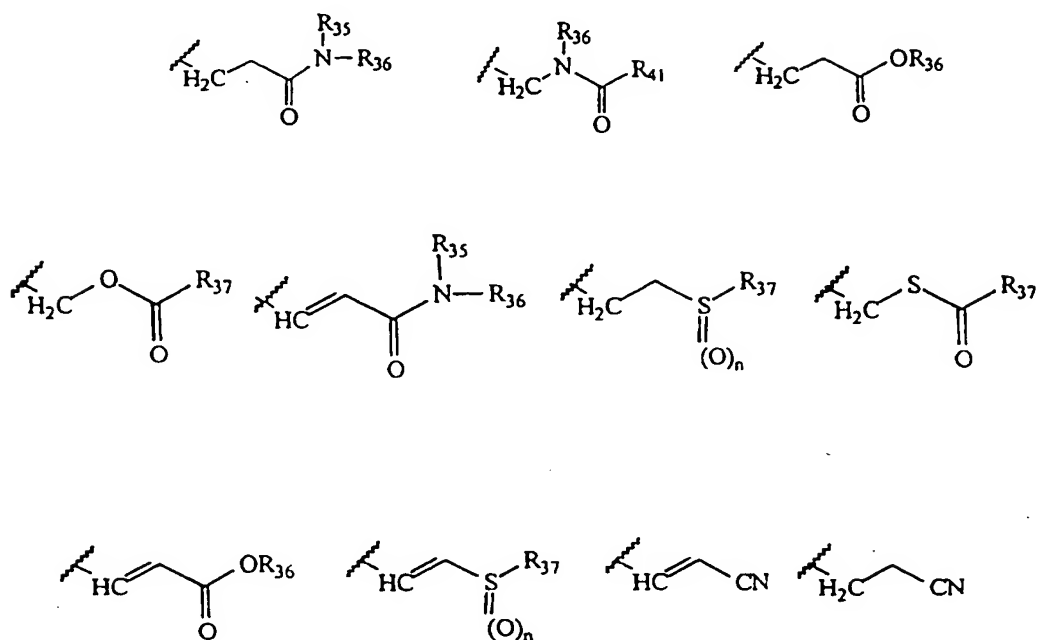
The present invention preferably relates to compounds of the formula II:



wherein

R_{31} is H, F or an alkyl group;

R_{32} is selected from one of the following moieties:



wherein

R_{35} is H, an alkyl group, an aryl group, $-\text{OR}_{38}$, or $-\text{NR}_{38}\text{R}_{39}$, and

R_{36} is H or an alkyl group,

or R_{35} and R_{36} , together with the atom(s) to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R_{41} is H, an alkyl group, an aryl group, $-OR_{38}$, $-SR_{39}$, $-NR_{38}R_{39}$, $-NR_{40}NR_{38}R_{39}$, or $-NR_{38}OR_{39}$, or R_{41} and R_{36} , together with the atom(s) to which they are attached, form a heterocycloalkyl group;

R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$;

wherein R_{38} , R_{39} , and R_{40} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or, wherein any two of R_{38} , R_{39} , and R_{40} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

n is 0, 1 or 2;

R_{33} is H or an alkyl group;

R_{34} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21} , R_{22} , R_{23} , and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21} , R_{22} , R_{23} , and R_{24} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or Z and Z_1 , both as defined above, together with the atoms to which they are bonded, form a heterocyclo alkyl group;

and pharmaceutically acceptable prodrugs, salts, and solvates thereof.

As used in the present application, the following definitions apply:

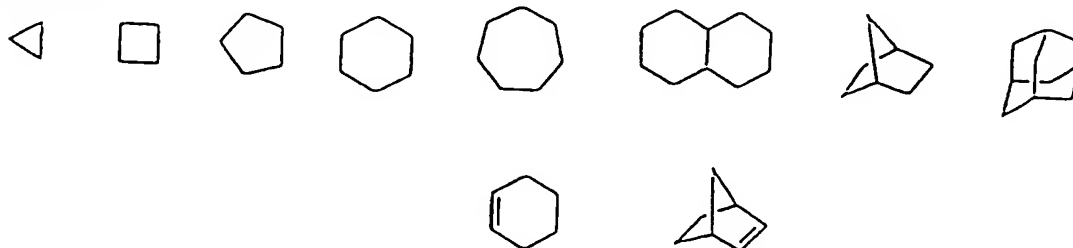
An "alkyl group" is intended to mean a straight or branched chain monovalent radical of saturated and/or unsaturated carbon atoms and hydrogen atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, pentenyl, butenyl, propenyl, ethynyl, butynyl, propynyl, pentynl, hexynyl, and the like, which may be unsubstituted (i.e., containing only carbon and hydrogen) or substituted by one or more suitable substituents as defined below.

A "cycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon ring atoms, each of which may be saturated or unsaturated, and which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more heterocycloalkyl groups, aryl groups, or heteroaryl groups, which

themselves may be unsubstituted or substituted by one or more suitable substituents.

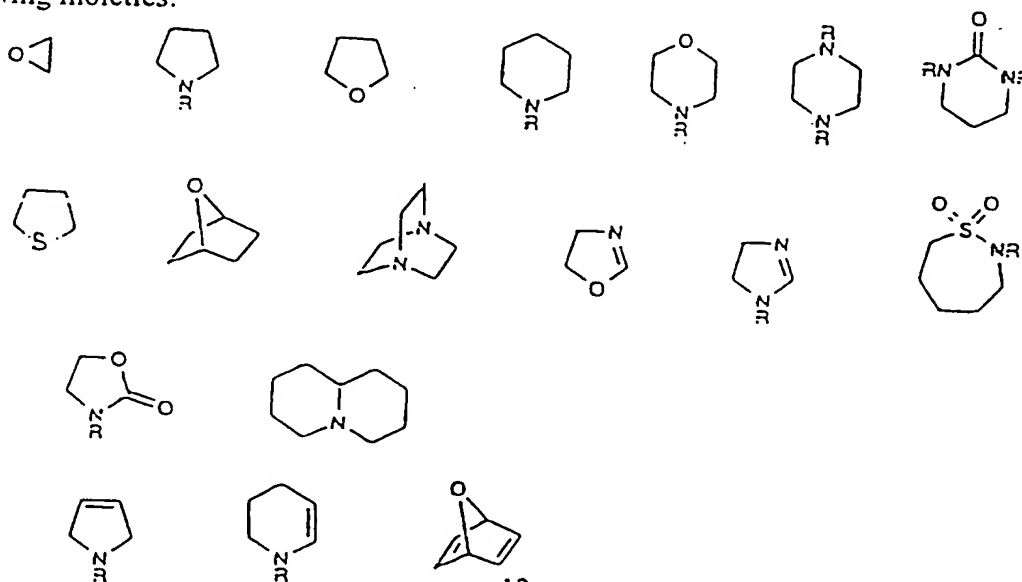
Illustrative examples of cycloalkyl groups include, but are not limited to, the following

moieties:



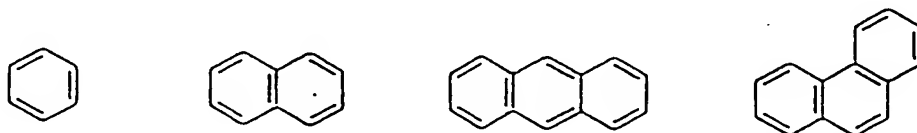
A "heterocycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or unsaturated, containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, and which includes 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen and sulfur, wherein the radical is unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents.

Illustrative examples of heterocycloalkyl groups include, but are not limited to the following moieties:

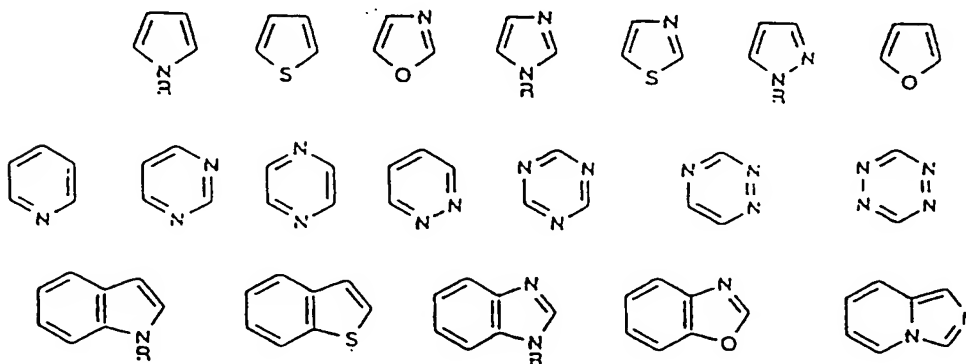


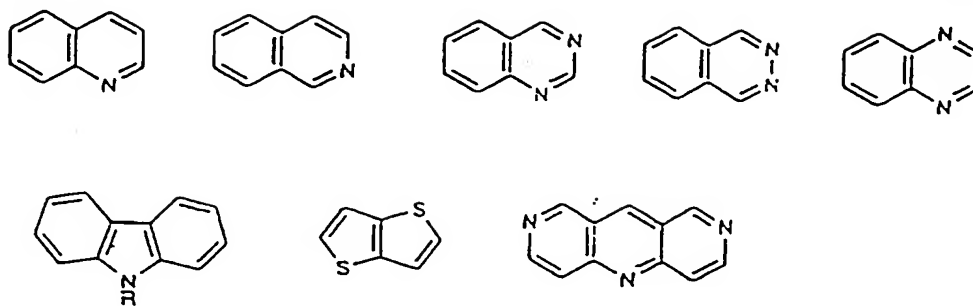
An "aryl group" is intended to mean an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 6, 10, 14, 18 carbon ring atoms, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents.

Illustrative examples of aryl groups include, but are not limited to, the following moieties:



A "heteroaryl group" is intended to mean an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, including 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or aryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heteroaryl groups include, but are not limited to, the following moieties:





An "acyl group" is intended to mean a $-C(O)-R$ radical, wherein R is any suitable substituent as defined below.

A "thioacyl group" is intended to mean a $-C(S)-R$ radical, wherein R is any suitable substituent as defined below.

A "sulfonyl group" is intended to mean a $-SO_2R$ radical, wherein R is any suitable substituent as defined below.

The term "suitable substituent" is intended to mean any of the substituents recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable substituents include, but are not limited to, hydroxy groups, oxo groups, alkyl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, aryloxy groups, heteroaryloxy groups, arylthio groups, heteroarylthio groups, and the like.

The term "suitable organic moiety" is intended to mean any organic moiety recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable organic moieties include, but are not limited to, hydroxy groups, alkyl groups, oxo groups,

cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, arylthio groups, heteroarylthio groups, and the like.

A "hydroxy group" is intended to mean the radical -OH.

An "amino group" is intended to mean the radical -NH₂.

An "alkylamino group" is intended to mean the radical -NHR where R is an alkyl group as defined above.

A "dialkylamino group" is intended to mean the radical -NR_aR_b where R_a and R_b are each independently an alkyl group as defined above.

An "alkoxy group" is intended to mean the radical -OR where R is an alkyl group as defined above, for example, methoxy, ethoxy, propoxy and the like.

An "alkoxycarbonyl group" is intended to mean the radical -C(O)OR where R is an alkyl group as defined above.

An "alkylsulfonyl group" is intended to mean the radical -SO₂R where R is an alkyl group as defined above.

An "alkylaminocarbonyl group" is intended to mean the radical -C(O)NHR where R is an alkyl group as defined above.

A "dialkylaminocarbonyl group" is intended to mean the radical -C(O)NR_aR_b where R_a and R_b are each independently an alkyl group as defined above.

A "mercapto group" is intended to mean the radical -SH.

An "alkylthio group" is intended to mean the radical -SR where R is an alkyl group as defined above.

A "carboxy group" is intended to mean the radical -C(O)OH.

A "carbamoyl group" is intended to mean the radical -C(O)NH₂.

An "aryloxy group" is intended to mean the radical -OR_c where R_c is an aryl group as defined above.

A "heteroaryloxy group" is intended to mean the radical -OR_d where R_d is a heteroaryl group as defined above.

An "arylthio group" is intended to mean the radical -SR_c where R_c is an aryl group as defined above.

A "heteroarylthio group" is intended to mean the radical -SR_d where R_d is a heteroaryl group as defined above.

A "pharmaceutically acceptable prodrug" is intended to mean a compound that may be converted under physiological conditions or by solvolysis to a compound of formula I or formula II.

A "pharmaceutically acceptable solvate" is intended to mean a solvate that retains the biological effectiveness and properties of the biologically active components of compounds of formulas I and II.

Examples of pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness and properties of the free acids and bases of compounds of formulas I and II and that is not biologically or otherwise undesirable.

Examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acids such as glucuronic acid and galacturonic acid, alpha-hydroxy acids such as citric acid and tartaric acid, amino acids such as aspartic acid and glutamic acid, aromatic acids such as benzoic acid and cinnamic acid, sulfonic acids such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal or alkaline earth metal hydroxide or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary and tertiary amines, and cyclic amines such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention.

The inventive compounds may exist as single stereoisomers, racemates and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention.

Preferably, the inventive compounds are used in optically pure form.

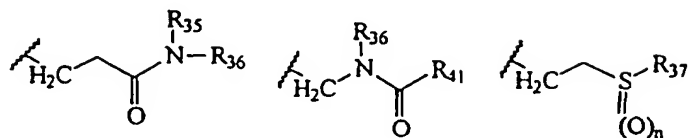
As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound which comprises at least a sufficient amount of a single enantiomer to yield a compound having the desired pharmacological activity. Preferably, "optically pure" is intended to mean a compound that comprises at least 90% of a single isomer (80% enantiomeric excess), preferably at least 95% (90% e.e.), more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

Preferably in the above formulas I and II, R_1 and R_{31} are H or F. Preferably in formula I, R_4 is an acyl group or a sulfonyl group. Preferably in formulas I and II, D_1 and D_2 are $-OR_{25}$, $=O$, $=S$, $\equiv N$, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group, and more preferably D_1 and D_2 are $=O$. Preferably A_1 and A_2 are C, CH, S, or S(O), and more preferably A_1 and A_2 are C.

Preferably B_1 and B_2 are $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or wherein R_{17} and R_{18} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group.

Preferably Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$; wherein R_{21} , R_{22} , and R_{23} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein any two of R_{21} , R_{22} , and R_{23} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group, or Z and Z_1 , together with the atoms to which they are attached, form a heterocycloalkyl group.

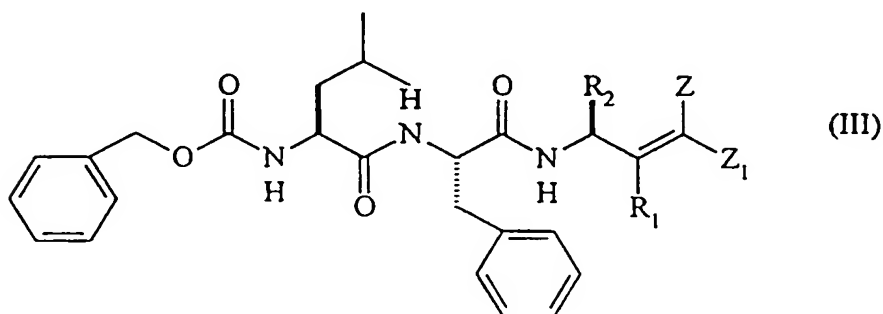
Preferably R_{32} is one of the following moieties:



wherein R_{35} , R_{36} , R_{37} , R_{41} and n are as defined above.

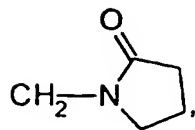
Compounds according to formula I include the following, where * indicates point of attachment:

Compounds 2, 3, 4, 5, 7, 11, 12, 13, 14, 16, 17, 18, 19, 21, 22, 24, 25, 41-43, 74, and 75 having the formula III:



2. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCPH}_3$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$,
3. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$,
4. R_2 is $\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$,

5. R_2 is



R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

7. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is CO_2CH_3 , and Z_1 is H

11. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is CO_2CH_3

12. R_2 is $\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

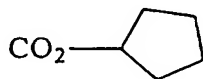
13. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{CH}_3$

14. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is CN

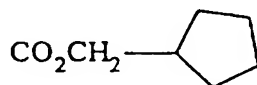
16. R_2 is $\text{CH}_2\text{NHC}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

17. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}(\text{CH}_3)_2$

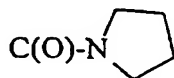
18. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



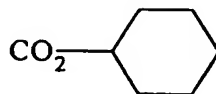
19. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



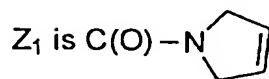
21. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



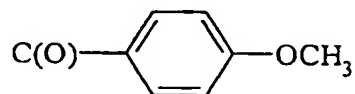
22. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$
24. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{Ph}$
25. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_1 is H, Z is H, and Z_1 is



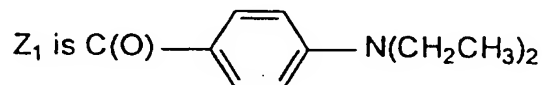
41. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z is H; and



42. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is

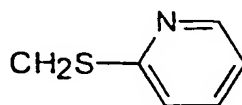


43. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z is H; and

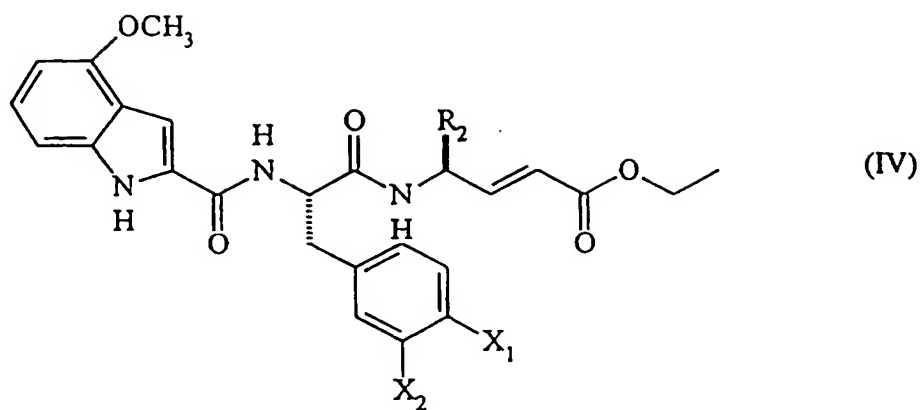


74. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z is H; and Z_1 is CH_2Cl

75. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z is H; and Z_1 is



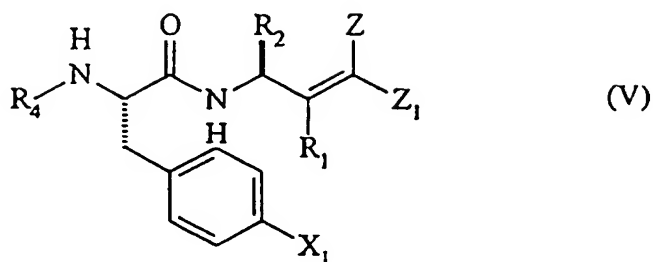
Compounds (26, 27, and 28) having the formula IV:



where X_1 and X_2 independently are H, F, or Cl,

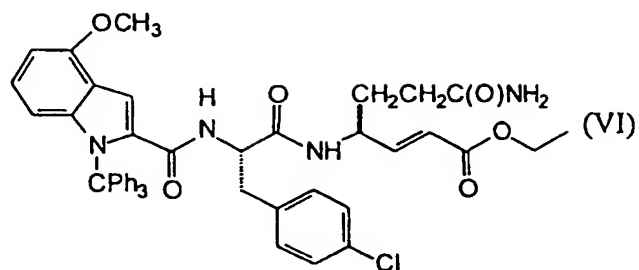
- 26. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, X_1 is Cl and X_2 is H
- 27. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, X_1 is F and X_2 is H
- 28. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, X_1 is H and X_2 is F

Compounds (30-34) having the formula V:

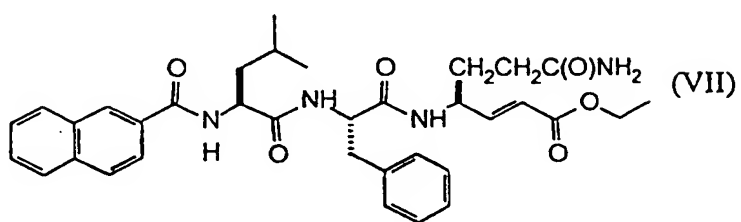


30. R_4 is $\text{PhCH}_2\text{OC(O)}$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
31. R_4 is $\text{CH}_3\text{CH}_2\text{CH}_2\text{SO}_2$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
32. R_4 is PhCH_2SO_2 , X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
33. R_4 is $\text{CH}_3\text{CH}_2\text{SO}_2$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
34. R_4 is PhSO_2 , X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

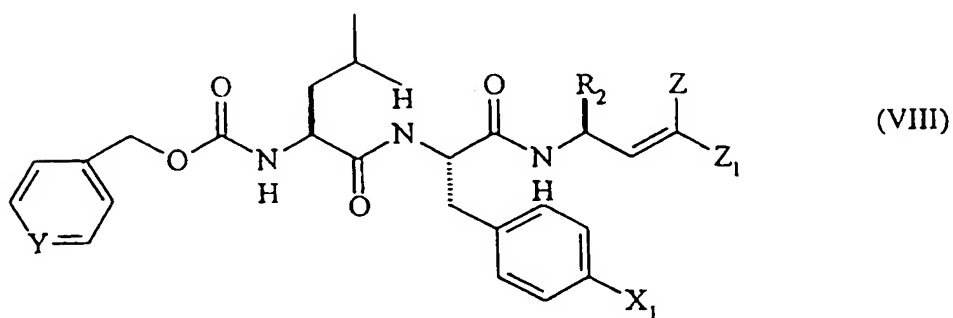
Compound 29 having the formula VI:



Compound 44 having the formula VII:



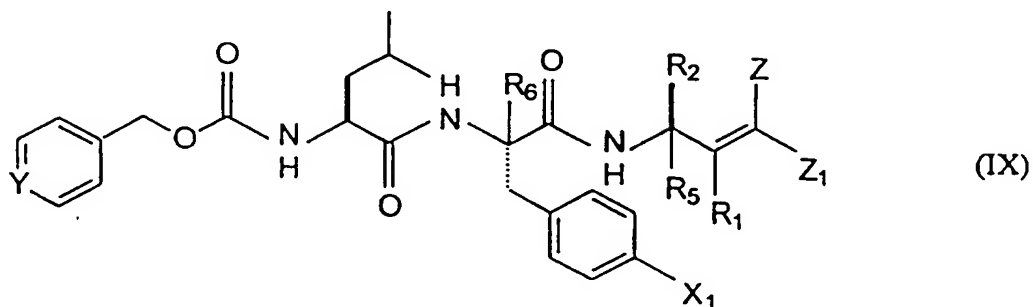
Compounds (35-37) having the formula VIII:



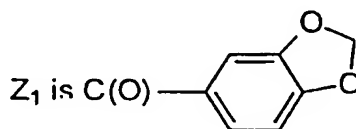
35. X_1 is F, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Y is CH, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
36. X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Y is N, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

37. X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, Y is CH, Z is H, and Z_1 is $\text{C(O)N(CH}_3\text{)OCH}_3$,

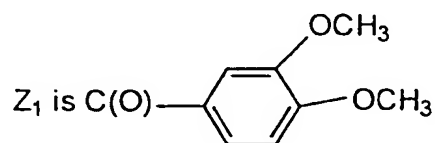
Compounds 46-66 and 78 having the formula IX:



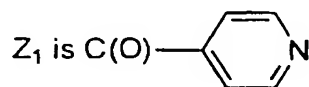
46. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$; R_5 , R_6 , and X_1 are H; Y is CH; Z is H; and



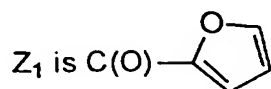
47. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$; R_5 , R_6 and X_1 are H; Y is CH; Z is H; and



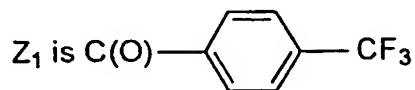
48. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$; R_5 , R_6 , and X_1 are H; Y is CH; Z is H; and



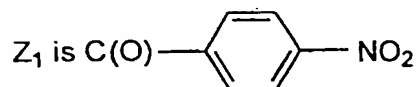
49. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



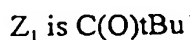
50. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



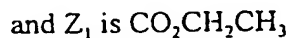
51. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



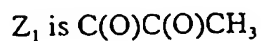
52. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



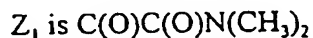
53. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 and R_6 are H; X_1 is OH; Y is CH; Z is H; and



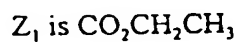
54. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



55. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and

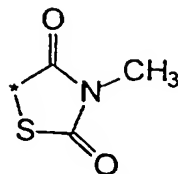


56. R_1 is H; R_2 is $\text{CH}_2\text{OC}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and



57. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and

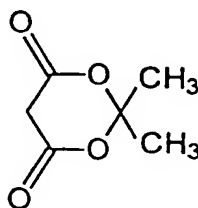
Z and Z_1 together form



where the S is preferably trans to the R_1 group

58. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; and Z and Z_1

together form



59. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and

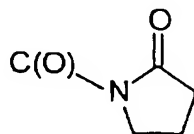
Z_1 is $\text{C}(\text{O})\text{NHPh}$

60. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and

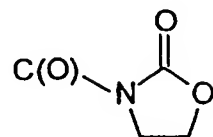
Z_1 is $\text{C}(\text{O})\text{N}(\text{CH}_3)\text{Ph}$

61. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; and

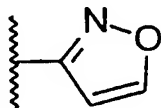
Z_1 is



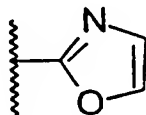
62. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 , R_6 , and X_1 are H; Y is CH; Z is H; Z_1 is



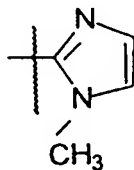
63. R_1 , R_5 , R_6 , X_1 , and Z are H; Y is CH; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and Z_1 is



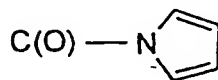
64. R_1 , R_5 , R_6 , X_1 , and Z are H; Y is CH; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and Z_1 is



65. R_1 , R_5 , R_6 , X_1 , and Z are H; Y is CH; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and Z_1 is

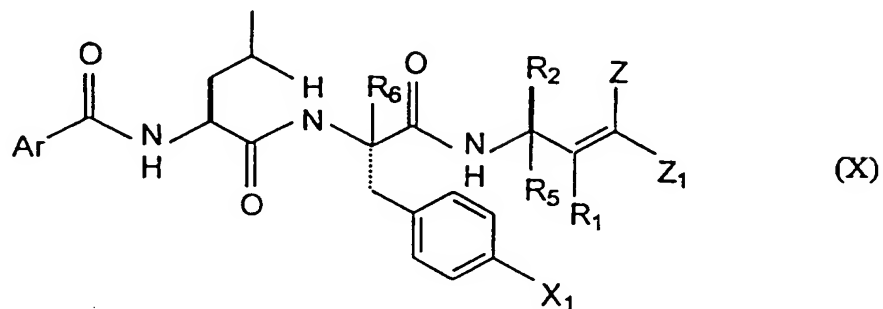


66. R_1 , R_5 , R_6 , X_1 , and Z are H; Y is CH; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and Z_1 is

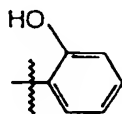


78. R_1 , R_5 , R_6 and X_1 are H; Y is CH; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z is CH_2Cl ; and Z_1 is H

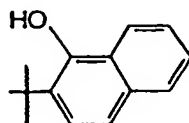
Compounds 67-69 having the formula X:



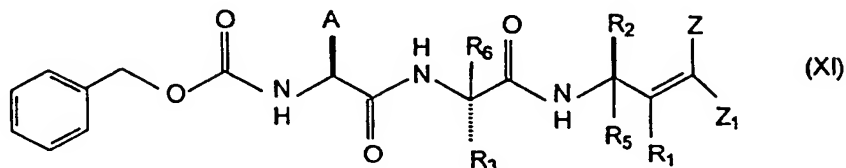
67. R_1 , R_5 , R_6 , X_1 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and Ar is Ph
68. R_1 , R_5 , R_6 , X_1 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z_1 is CO_2CH_3 ; and Ar is



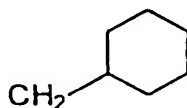
69. R_1 , R_5 , R_6 , X_1 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and Ar is



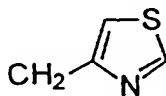
Compounds 70-73 having the formula XI:



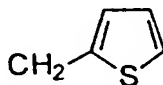
70. R_1 , R_5 , R_6 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is CH_2Ph ; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and A is



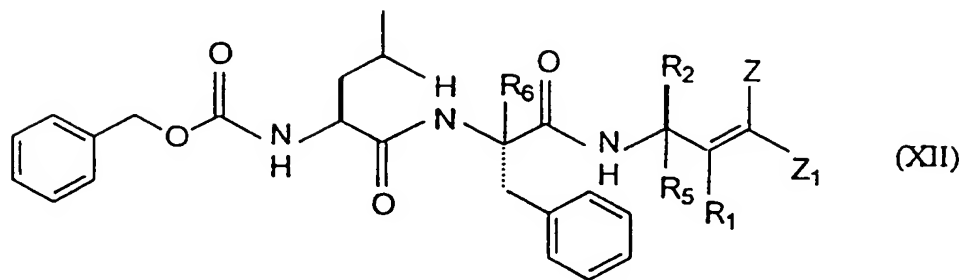
71. R_1 , R_5 , R_6 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is CH_2Ph ; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and A is Ph
72. R_1 , R_5 , R_6 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; A is $\text{CH}_2\text{CH}(\text{CH}_3)_2$; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and R_3 is



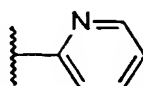
73. R_1 , R_5 , R_6 , and Z are H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; A is $\text{CH}_2\text{CH}(\text{CH}_3)_2$; Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; and R_3 is



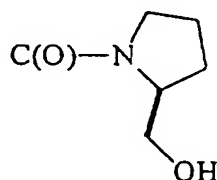
Compounds 1, 6, 8-10, 15, 20, 23, 38-40, 76, and 77 having the formula XII:



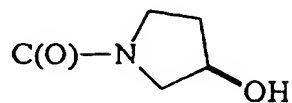
1. R₁ is H; R₂ is CH₂CH₂CN; R₃ is H; R₆ is H; Z is F; and Z₁ is CO₂CH₂CH₃
6. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is C(O)NHCH₂CH₃
8. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is F; and Z₁ is CO₂CH₂CH₃
9. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is SO₂CH₃
10. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is SO₂Ph
15. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is CO₂H
20. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is PO(OCH₂CH₃)₂
23. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is



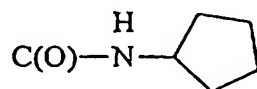
38. R₁ is H; R₂ is CH₂CH₂C(O)NH₂; R₃ is H; R₆ is H; Z is H; and Z₁ is



39. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is H; R_6 is H; Z is H; and Z_1 is

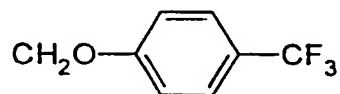


40. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is H; R_6 is H; Z is H; and Z_1 is



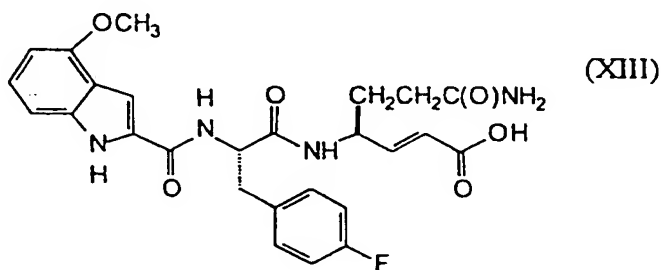
76. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is H; R_6 is H; Z is H; and Z_1 is CH_2OAc

77. R_1 is H; R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; R_3 is H; R_6 is H; Z is H; and Z_1 is

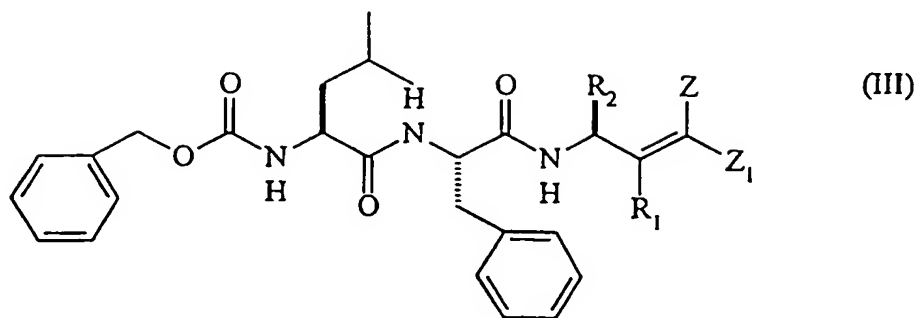


Compound 45 having the formula XIII:

45.

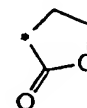


Compounds 79-97, also having the formula III:



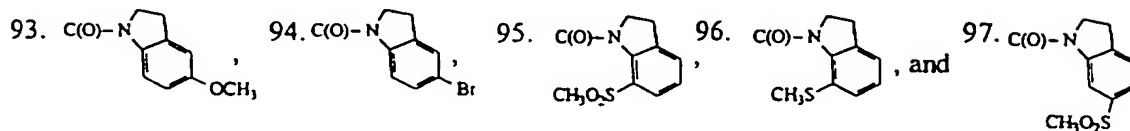
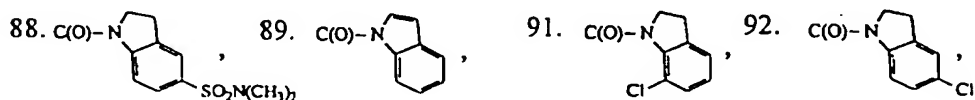
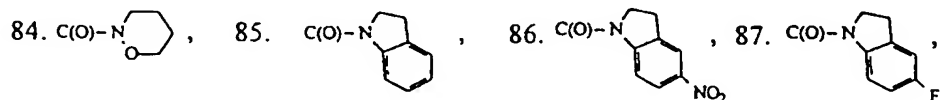
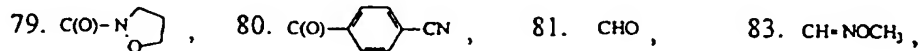
82. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is CH_3 and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$.

90. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, and Z and Z_1 together form

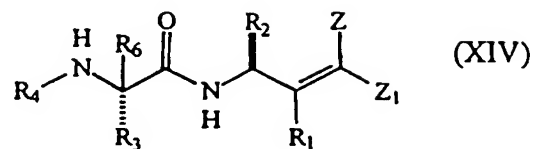


where C=O is preferably cis to the R_1 group

or wherein R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is selected from:

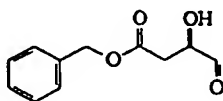


Compounds 98-121 having formula XIV:

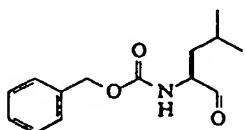


wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and

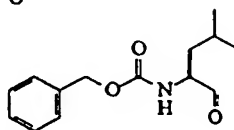
98. R_3 is CH_2Ph and R_4 is



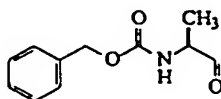
99. R_3 is H and R_4 is



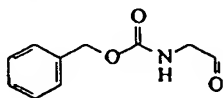
100. R_3 is CH_2 --OAc and R_4 is

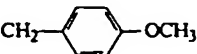


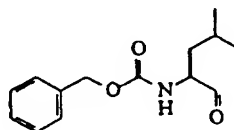
101. R_3 is CH_2Ph and R_4 is



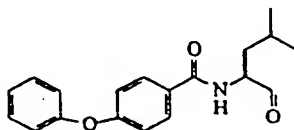
102. R_3 is CH_2Ph and R_4 is

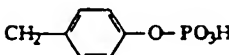


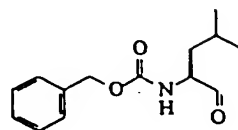
103. R_3 is CH_2 --OCH₃ and R_4 is



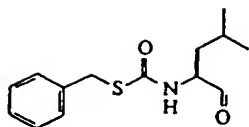
104. R_3 is CH_2Ph and R_4 is



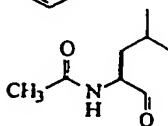
105. R_3 is CH_2 --O-PO₃H and R_4 is



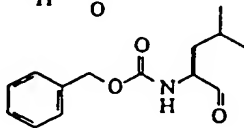
106. R_3 is CH_2Ph and R_4 is



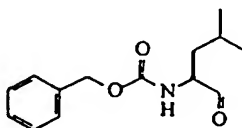
107. R_3 is CH_2Ph and R_4 is



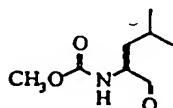
108. R_3 is CH_2CH_3 and R_4 is



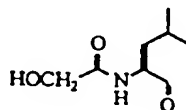
109. R_3 is CH_3 and R_4 is

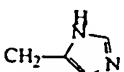


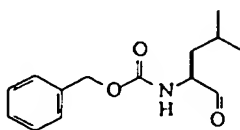
110. R_3 is CH_2Ph and R_4 is

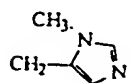


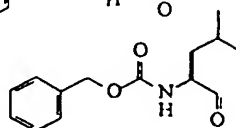
111. R_3 is CH_2Ph and R_4 is



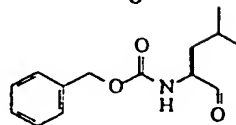
112. R_3 is CH_2 - and R_4 is



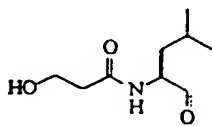
113. R_3 is CH_2 - and R_4 is



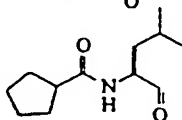
114. R_3 is CH_2 -- CH_2OH and R_4 is



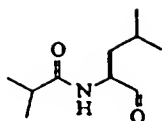
115. R_3 is CH_2Ph and R_4 is



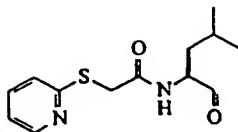
116. R_3 is CH_2Ph and R_4 is



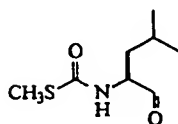
- 117.
- R_3
- is
- CH_2Ph
- and
- R_4
- is



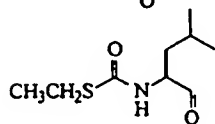
- 118.
- R_3
- is
- CH_2Ph
- and
- R_4
- is



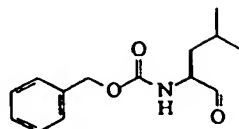
- 119.
- R_3
- is
- CH_2Ph
- and
- R_4
- is



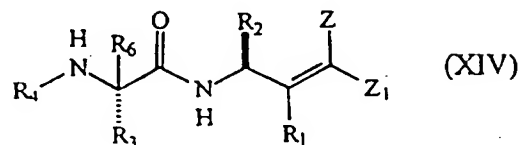
- 120.
- R_3
- is
- CH_2Ph
- and
- R_4
- is



- 121.
- R_3
- is
- $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
- and
- R_4
- is

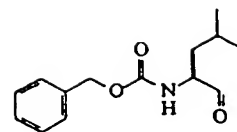


Compounds 122-130, also having the formula XIV:

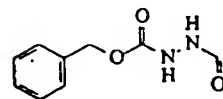


wherein R_6 is H, R_1 is H, R_3 is CH_2Ph and

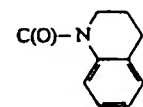
- 122.
- R_2
- is
- $\text{CH}_2\text{OC(O)NHC(O)CH}_2\text{Cl}$
- , Z is H,
- Z_1
- is
- $\text{CO}_2\text{CH}_2\text{CH}_3$
- and
- R_4
- is



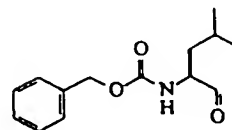
- 123.
- R_2
- is
- $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$
- , Z is H,
- Z_1
- is
- $\text{CO}_2\text{CH}_2\text{CH}_3$
- and
- R_4
- is

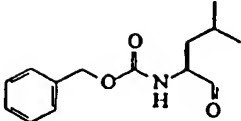
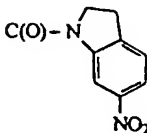
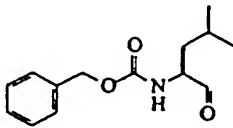
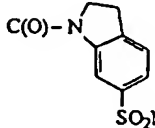
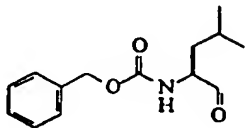
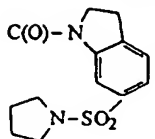
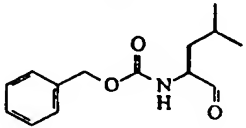
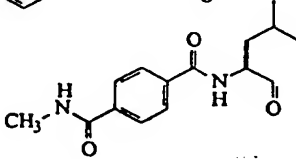

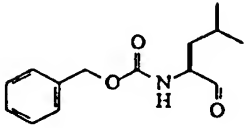


- 124.
- R_2
- is
- $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$
- , Z is H,
- Z_1
- is



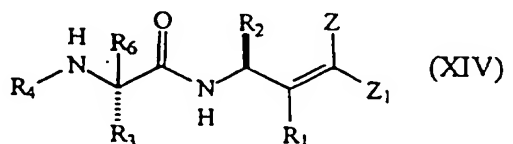
and R_4 is




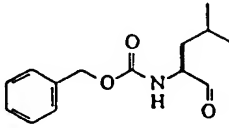
125. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is NO_2 , and R_4 is 
126. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is  and R_4 is 
127. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is  and R_4 is 
128. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is  and R_4 is 
129. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
130. R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z and Z_1 together form  and R_4 is 

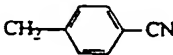
where $\text{C}=\text{O}$ is preferably cis to the R_1 group.

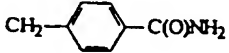
Compounds 131-145, also having the formula XIV:





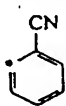


wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_4 is

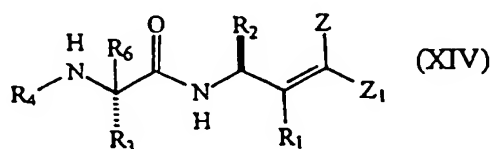
131. R_3 is CH_2Ph , Z is H and Z_1 is   and

132. R_3 is , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

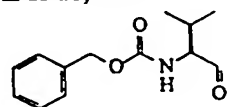
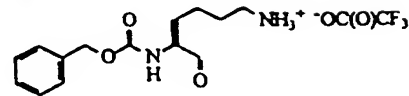
133. R_3 is , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

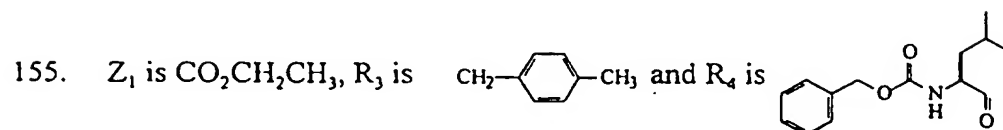
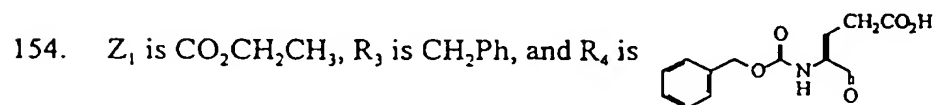
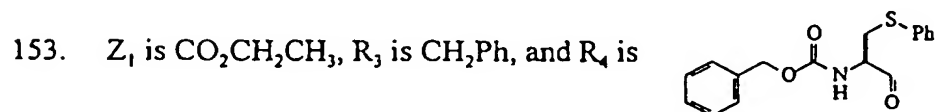
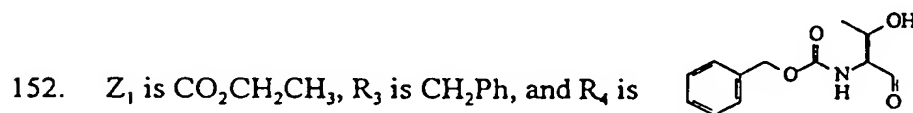
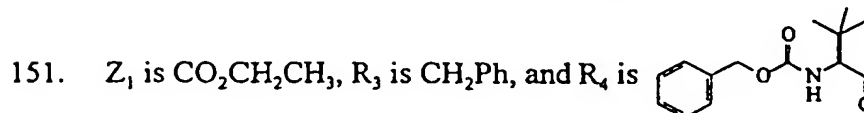
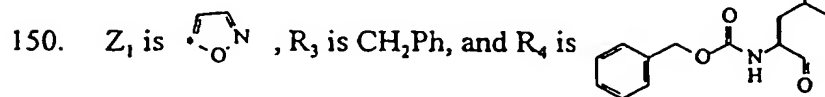
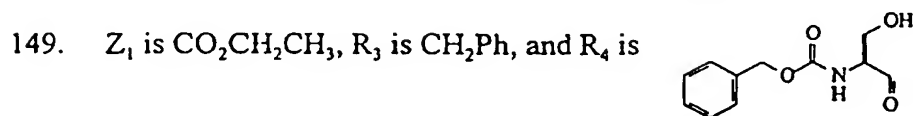
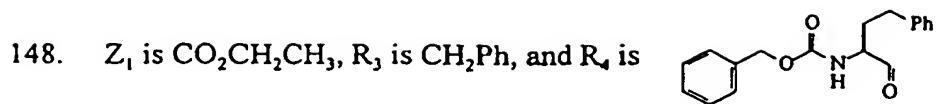
134. R_3 is $\text{CH}(\text{OH})\text{CH}_3$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
135. R_3 is CH_2 -, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
136. R_3 is CH_2 -- OCH_2CH_3 , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
137. R_3 is $\text{CH}_2\text{CH}_2\text{CH}_3$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
138. R_3 is CH_2Ph , Z is H and Z_1 is $\text{C}(\text{O})\text{N}(\text{OH})\text{CH}_3$
139. R_3 is CH_2 -- $\text{CH}_2\text{CH}_2\text{OH}$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
140. R_3 is CH_2 -- CH_2OCH_3 , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
141. R_3 is $\text{CH}_2\text{CH}(\text{CH}_3)_2$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
142. R_3 is CH_2SCH_3 , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
143. R_3 is $\text{CH}_2\text{SCH}_2\text{CH}_3$, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$
144. R_3 is CH_2Ph , Z is CH_3 , and Z_1 is CO_2H ,
145. R_3 is CH_2Ph , Z is H, and Z_1 is 

Compounds 146-155, also having the formula XIV:

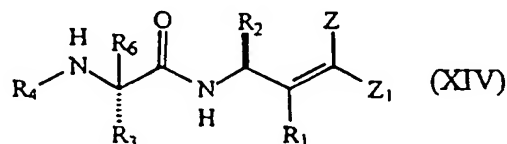


wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, and

146. Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is 
147. Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is 

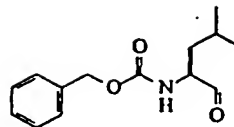


Compounds 156-173, also having formula XIV:

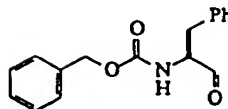


wherein R_6 is H, R_3 is CH_2Ph , R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and

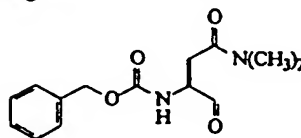
156. R_1 is OH, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



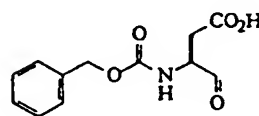
157. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is

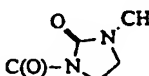


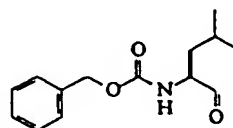
158. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



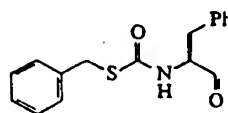
159. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



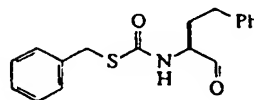
160. R_1 is H, Z is H, Z_1 is , and R_4 is



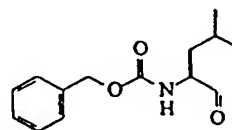
161. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



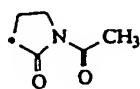
162. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



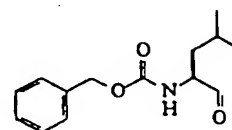
163. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{C}(\text{CH}_3)_3$, and R_4 is



164. R_1 is H, Z and Z_1 together form

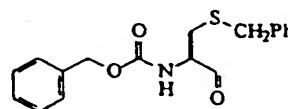


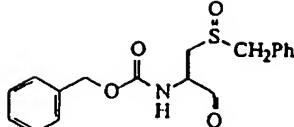
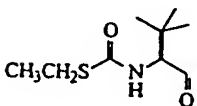
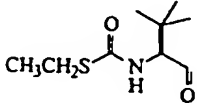
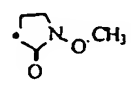
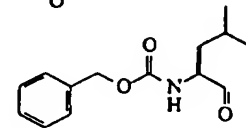
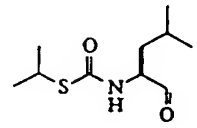
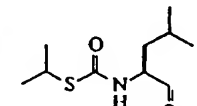
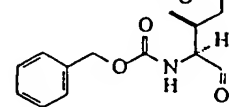
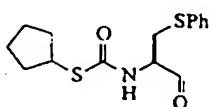
and R_4 is



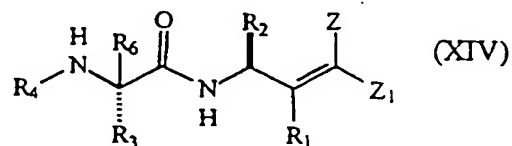
where C=O is preferably cis to the R_1 group

165. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is

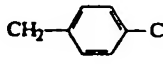
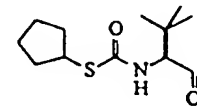


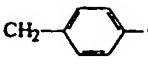
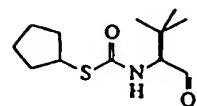
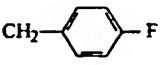
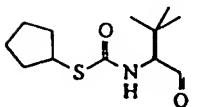
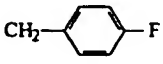
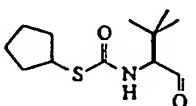
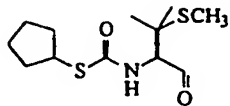
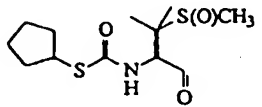
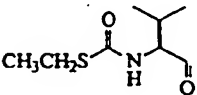
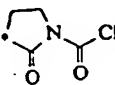
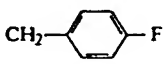
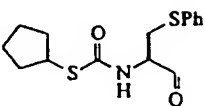
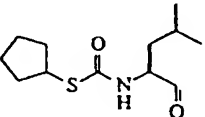
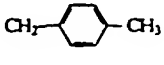
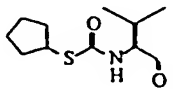
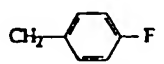
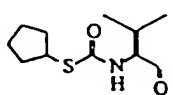
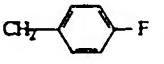
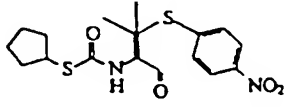
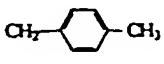
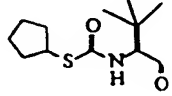
166. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
167. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
168. R_1 is H, Z is CH_3 , Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
169. R_1 is H, Z and Z_1 together form  and R_4 is 
- where C=O is preferably cis to R_1
170. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
171. R_1 is H, Z is CH_3 , Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
172. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 
173. R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is 

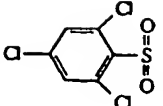
Compounds 174-188, also having the formula XIV:


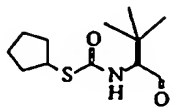


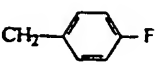
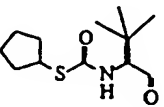
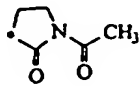
wherein R_6 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, and

174. Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is , and R_4 is 


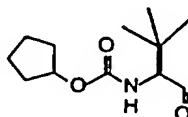
175. Z is CH₃, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
176. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
177. Z is CH₃, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
178. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is CH₂Ph, and R₄ is 
179. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is CH₂Ph, and R₄ is 
180. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is CH₂Ph, and R₄ is 
181. Z and Z₁ together form , R₃ is , and R₄ is 
- where C=O is preferably cis to the R₁ group
182. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is CH₂Ph, and R₄ is 
183. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
184. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
185. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 
186. Z is H, Z₁ is CO₂CH₂Ph, R₃ is , and R₄ is 

187. Z is CH₃, Z₁ is CO₂CH₂CH₃, R₃ is CH₂Ph and R₄ is  is

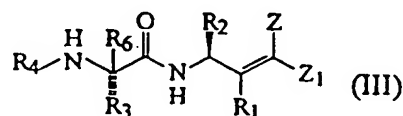
188. Z is H, Z₁ is CO₂CH₂CH₂OCH₃, R₃ is  and R₄ is 

189. R₃ is , R₄ is , and Z and Z₁ together form 

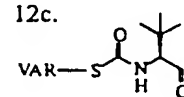
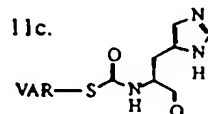
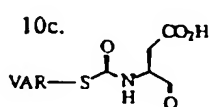
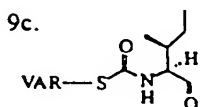
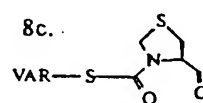
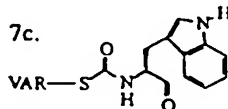
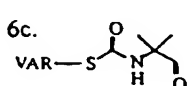
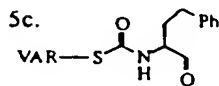
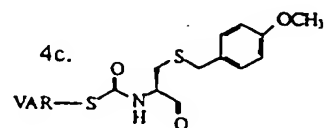
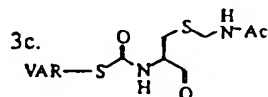
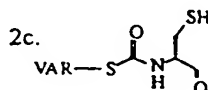
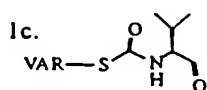
where C=O is preferably cis to the R₁ group

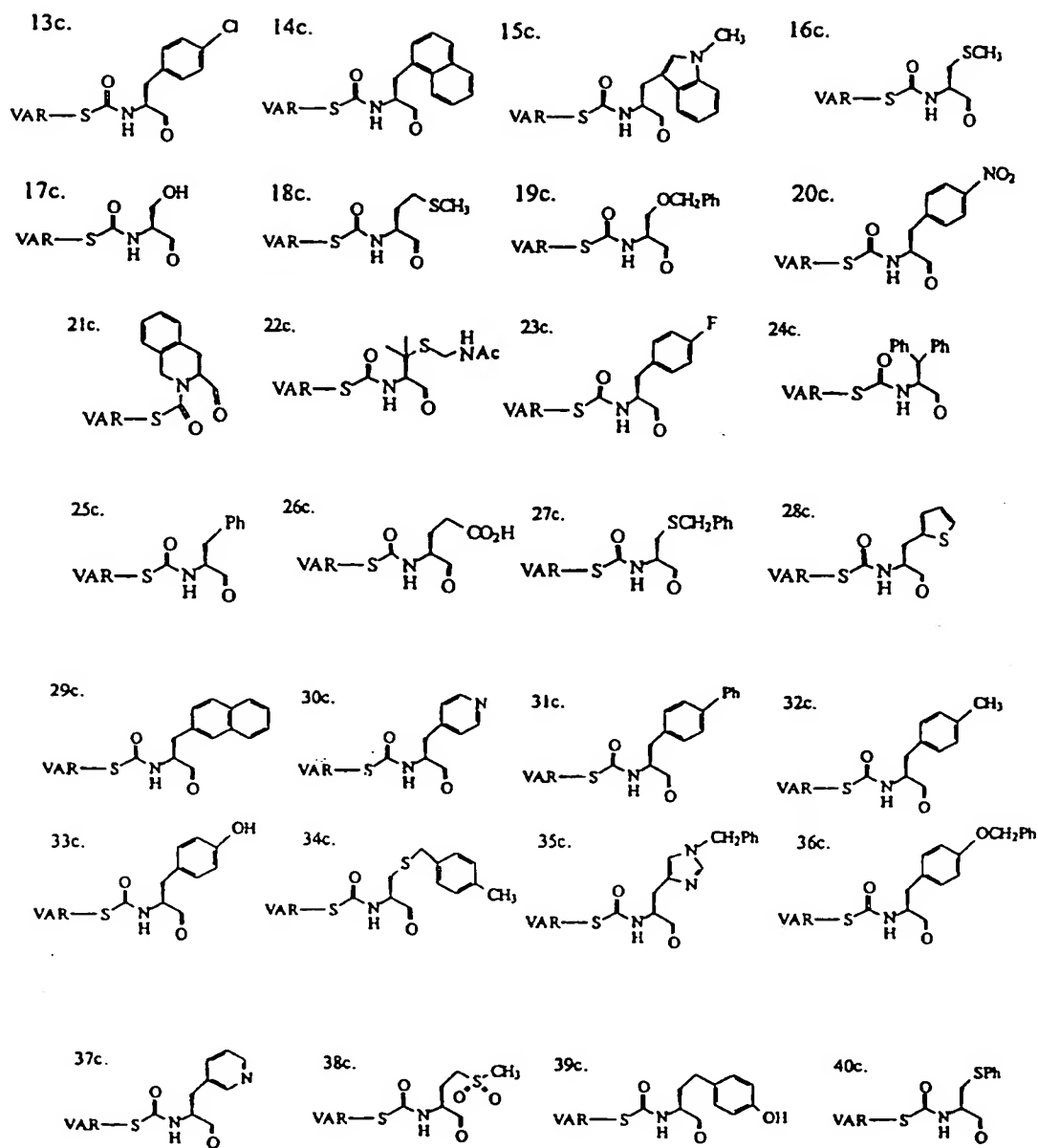
190. Z is H, Z₁ is CO₂CH₂CH₃, R₃ is , and R₄ is 

Other compounds according to the invention include the following compounds of formula III:

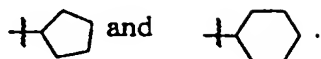


wherein R₆ is H, R₁ is H, R₃ is CH₂Ph, R₂ is CH₂CH₂C(O)NH₂, Z is H, Z₁ is CO₂CH₂CH₃, and R₄ is selected from the following:





wherein VAR is selected from $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-Ph}$,



The present invention is further directed to methods of inhibiting picornaviral 3C protease activity that comprises contacting the protease for the purpose of such inhibition with an effective amount of a compound of formula I or a pharmaceutically acceptable prodrug, salt, or solvate thereof. For example, one can inhibit picornaviral 3C protease activity in mammalian tissue by administering a compound of formula I or II or a pharmaceutically acceptable prodrug, salt, or solvate thereof. More particularly, the present invention is directed to methods of inhibiting rhinoviral protease activity.

The activity of the inventive compounds as inhibitors of picornaviral 3C protease activity may be measured by any of the methods available to those skilled in the art, including *in vivo* and *in vitro* assays. Examples of suitable assays for activity measurements include the Antiviral HI-HeLa Cell Culture Assay and the Normal Human Bronchial Epithelial Cell Assay, both described herein.

Administration of the compounds of the formulas I and II, or their pharmaceutically acceptable prodrugs, salts, and solvates, may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include, but are not limited to, oral, nasal, parenteral, topical, transdermal and rectal.

The inventive compounds of formulas I and II, and their pharmaceutically acceptable prodrugs, salts, and solvates, may be administered as a pharmaceutical composition in any suitable pharmaceutical form recognizable to the skilled artisan.

Suitable pharmaceutical forms include, but are not limited to, solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions and aerosols. The pharmaceutical composition may also include suitable excipients, diluents, vehicles and carriers, as well as other pharmaceutically active agents, depending upon the intended use.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known to those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating and compressing when necessary for tablet forms, or mixing, filling and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraural and/or rectal administration.

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulphate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers may include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g. solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of formula I or II or a pharmaceutically acceptable prodrug, salt, or solvate thereof) and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of 3C protease activity, by any known method of administering the dose including topical, for example, as an ointment or cream; orally, rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural or intraocular infusion.

A "therapeutically effective amount" is intended to mean that amount of a compound of formula I or II that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more picarnoviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus. The amount of a given compound of formula I or II that will correspond to a "therapeutically effective amount" will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, the identity of the mammal in need thereof, but can nevertheless be readily determined by one of skill in the art.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of one or more picarnoviral 3C proteases, such as human rhinoviruses, human poliovirus,

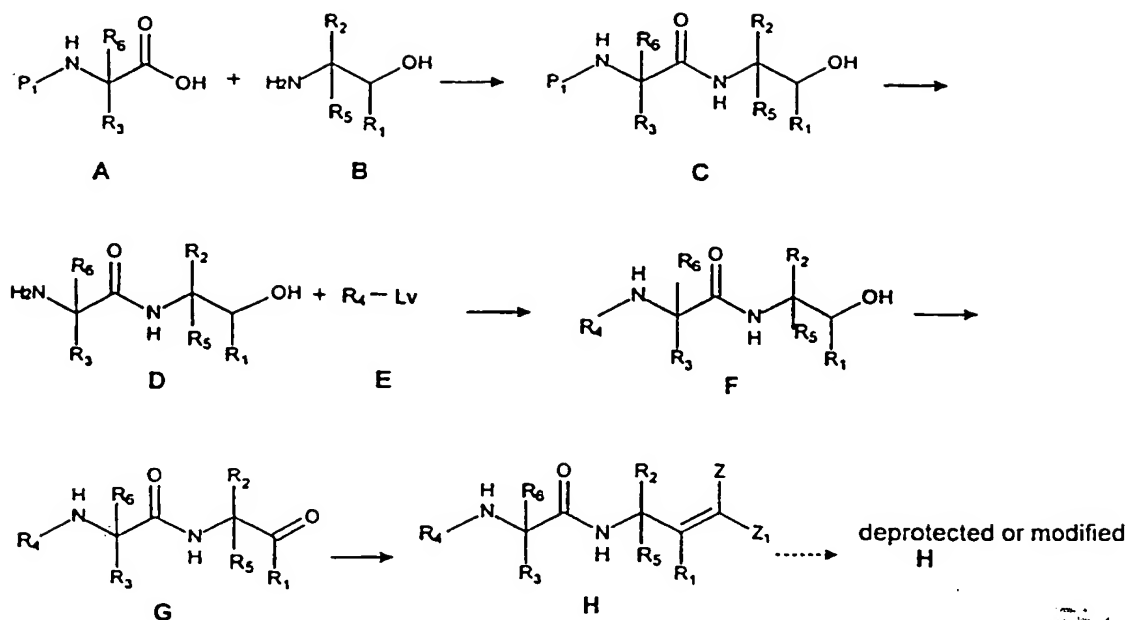
human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus, and includes:

- (a) prophylactic treatment in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but not yet diagnosed as having it;
- (b) inhibiting the disease condition; and/or
- (c) alleviating, in whole or in part, the disease condition.

The inventive compounds, and their salts, solvates, and prodrugs, may be prepared by employing the techniques available in the art using starting materials that are readily available. Certain novel and exemplary methods of preparing the inventive compounds are described below.

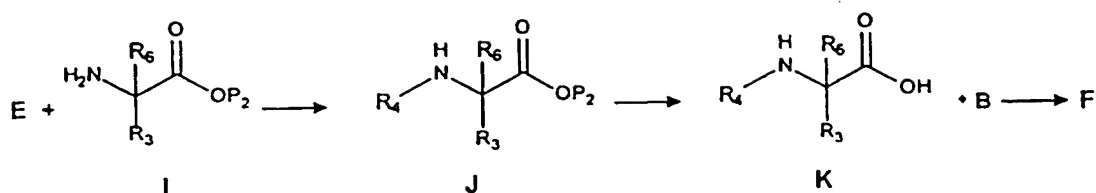
Preferably, the inventive compounds of formulas I and II are prepared by the novel methods of the present invention, including the four general methods shown below. In each of these general methods, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , Z , and Z_1 are as defined above.

General Method I:



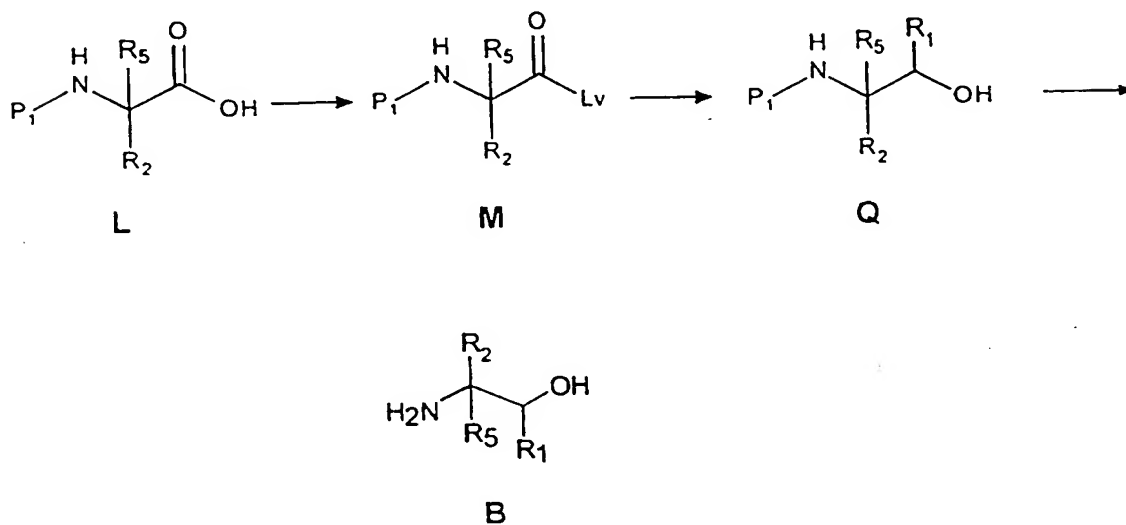
In General Method I, protected amino acid **A**, where P_1 is an appropriate protecting group for nitrogen, is subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to produce amide **C**. Amide **C** is then deprotected to give free amine (or salt thereof) **D**. Amine **D** and compound **E**, where "Lv" is an appropriate leaving group, are subjected to a bond forming reaction generating compound **F**. Compound **F** is oxidized to intermediate **G**, which is then transformed into unsaturated product **H**. If protecting groups are used on any R groups (R_1 - R_6) and/or on Z and/or Z_1 , product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

An alternative method to prepare intermediate **F** is described as follows:



Compound E and amino acid (or salt thereof) I, where P₂ is an appropriate protecting group for oxygen, are subjected to a bond forming reaction to produce intermediate J. Intermediate J is deprotected to yield free carboxylic acid K, which is subsequently subjected to an amide forming reaction with amino alcohol (or salt thereof) B to generate intermediate F.

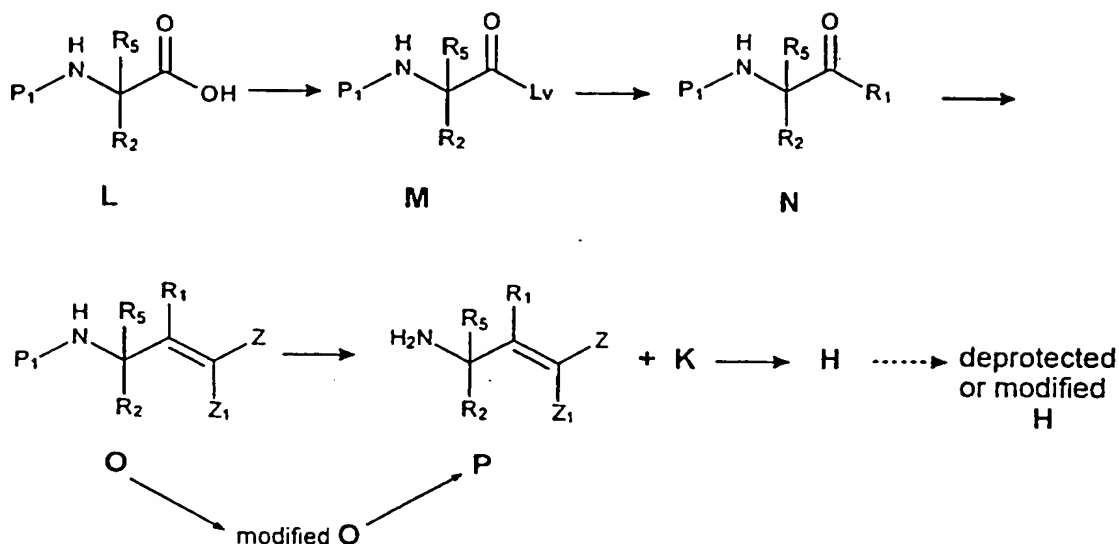
Amino alcohol B can be prepared as follows:



Amino acid L, where P₁ is an appropriate protecting group for nitrogen, is converted to carbonyl derivative M, where "Lv" is a leaving group. Compound M is subjected to a

reaction where "Lv" is reduced to protected amino alcohol Q. Amino alcohol Q is deprotected to give amino alcohol B.

General Method II:



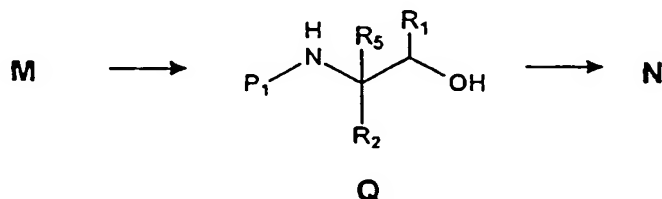
In General Method II, amino acid L, where P₁ is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative M, where "Lv" is a leaving group.

Compound M is subjected to a reaction where "Lv" is replaced by R₁ to give derivative N. Derivative N is then transformed into unsaturated product O. Unsaturated compound O is deprotected to give free amine (or salt thereof) P, or modified one or more times at R₂, R₅, Z and/or Z₁ to give one or more modified O compounds.

Modified O is then deprotected to give amine (or salt thereof) P. Amine P is subsequently subjected to an amide forming reaction with carboxylic acid K, prepared as described in General Method I, to give final product H. If protecting groups were used on

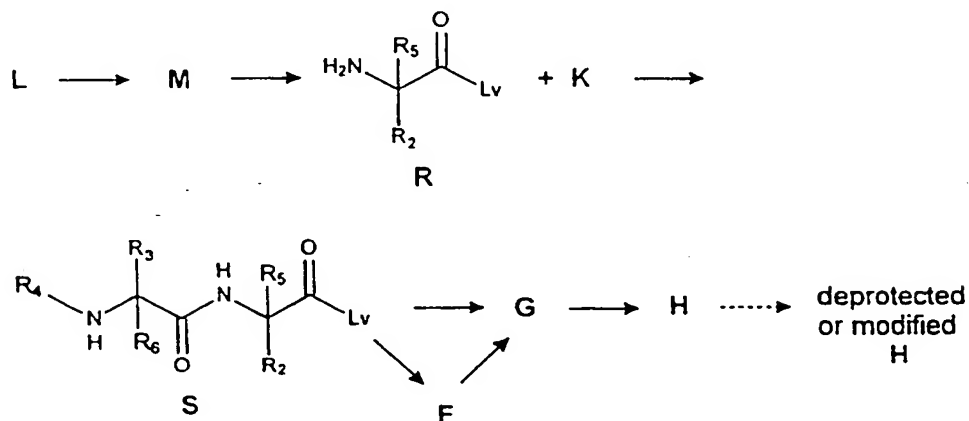
any R group (R_1 - R_6) and/or on Z and/or Z_1 , product H is deprotected and/or further modified to yield "deprotected or modified H."

An alternative method to prepare intermediate N is described as follows:



Compound M is subjected to a reaction where "Lv" is reduced to protected amino alcohol Q. Amino alcohol Q is subsequently oxidized to derivative N.

General Method III:

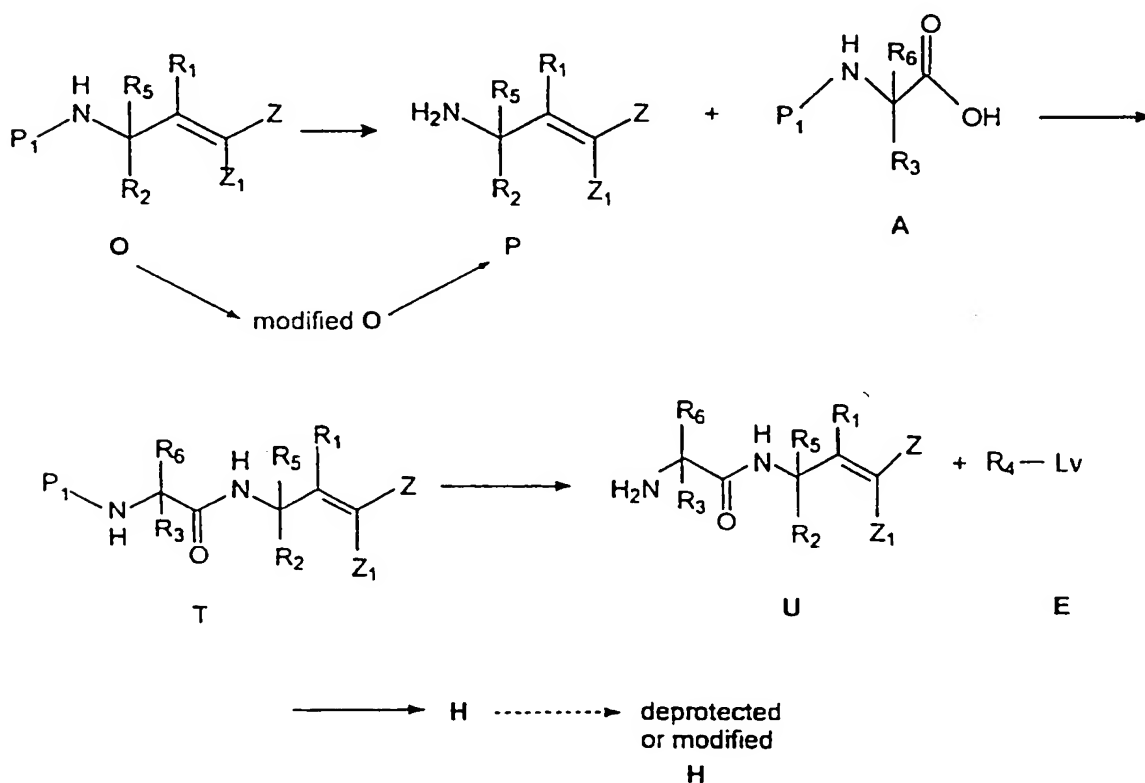


In General Method III, amino acid L, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative M, where "Lv" is a leaving group.

Derivative **M** is deprotected to give free amine (or salt thereof) **R**, which subsequently is subjected to an amide forming reaction with carboxylic acid **K** to give intermediate **S**.

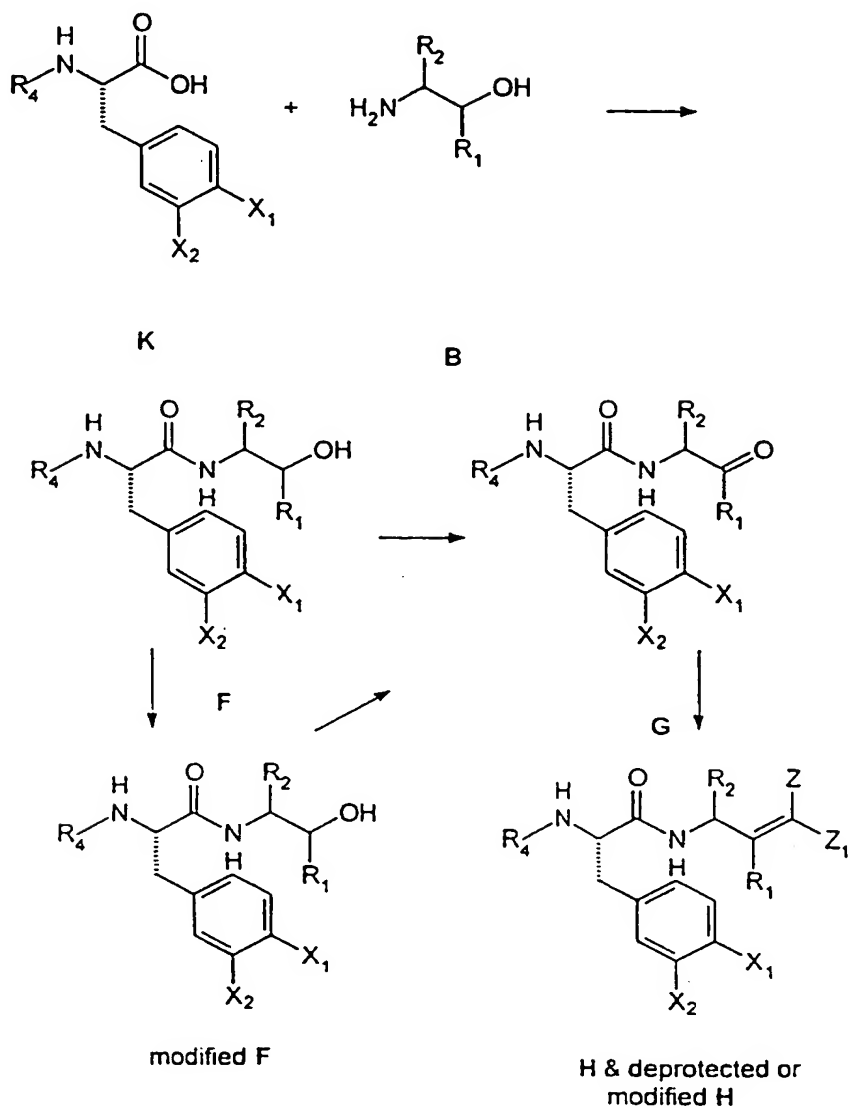
Intermediate **S** is then either converted directly to carbonyl intermediate **G**, or successively reduced to alcohol **F**, which is then oxidized to **G**. Intermediate **G** is subjected to a reaction to yield the unsaturated final product **H**. If protecting groups were used on any **R** groups (**R**₁-**R**₆) and/or on **Z** and/or **Z**₁, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

General Method IV:



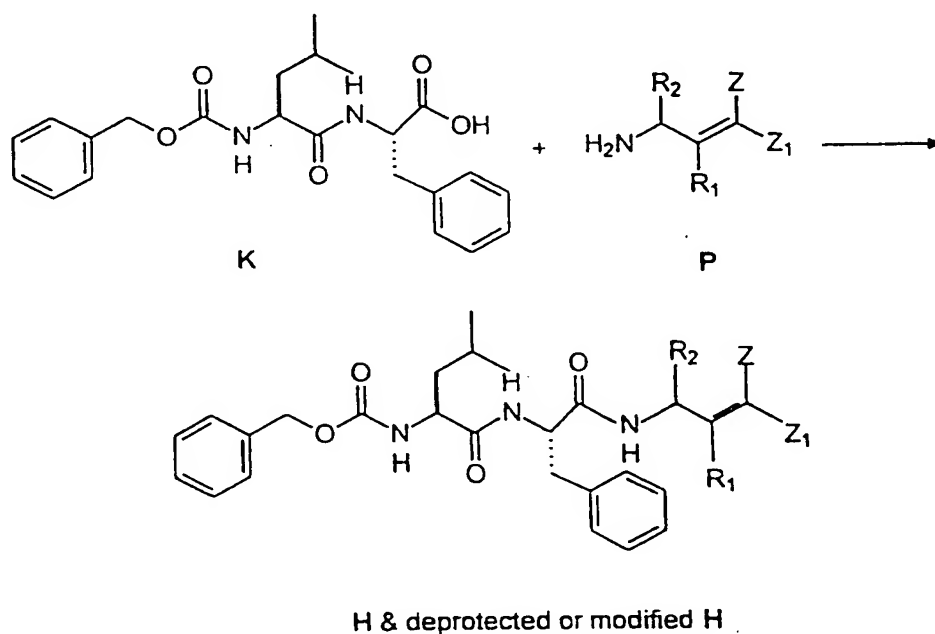
In General Method IV, free amine (or salt thereof) P, prepared from intermediate O as described in General Method II, is converted to amide T by reaction with amino acid A, where P_i is an appropriate protecting group for nitrogen. Compound T is further deprotected to free amine (or salt thereof) U, which is subsequently converted to H with reactive intermediate E. If protecting groups were used on any R groups (R₁-R₆) and/or on Z and/or Z_i, product H is deprotected and/or further modified to yield "deprotected or modified H."

Preferably the compound of formulas I or II can be prepared by one of four specific methods. For example, compounds 4, 12, 14, 16, 20, 23, 24, 26-30, 35, and 36 can be prepared by Specific Method I:



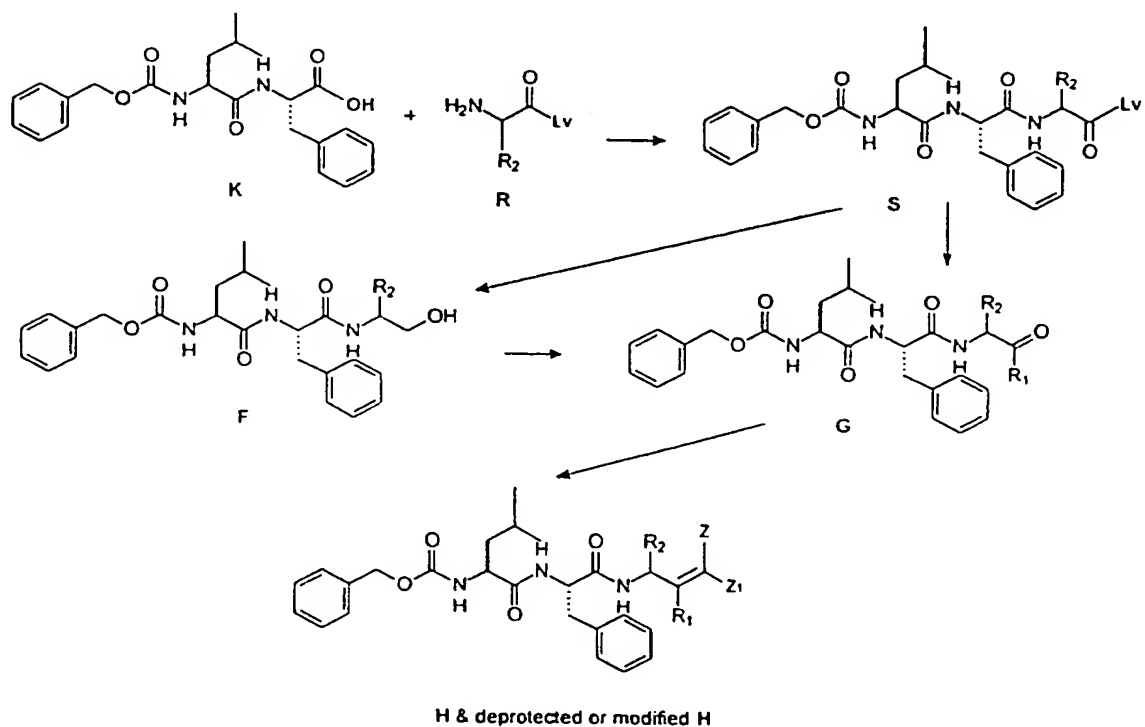
In Specific Method I, carboxylic acid **K**, CBZ-L-Leu-L-Phe, which can be purchased from Bachem or prepared as described in General Method I, is subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to generate intermediate **F**. Intermediate **F** is oxidized to intermediate **G**, which is then transformed into unsaturated product **H**. In the case of Compound 12, intermediate **F** is oxidized to modified **F**, which is then oxidized to intermediate **G**. If protecting groups were used on any R groups (R_1 - R_6) and/or on Z and/or Z_1 , product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

For example, compounds 1-3, 6-11, 17-19, 21, 22, 25, 37-40, and 74-77 can be prepared by Specific Method II:



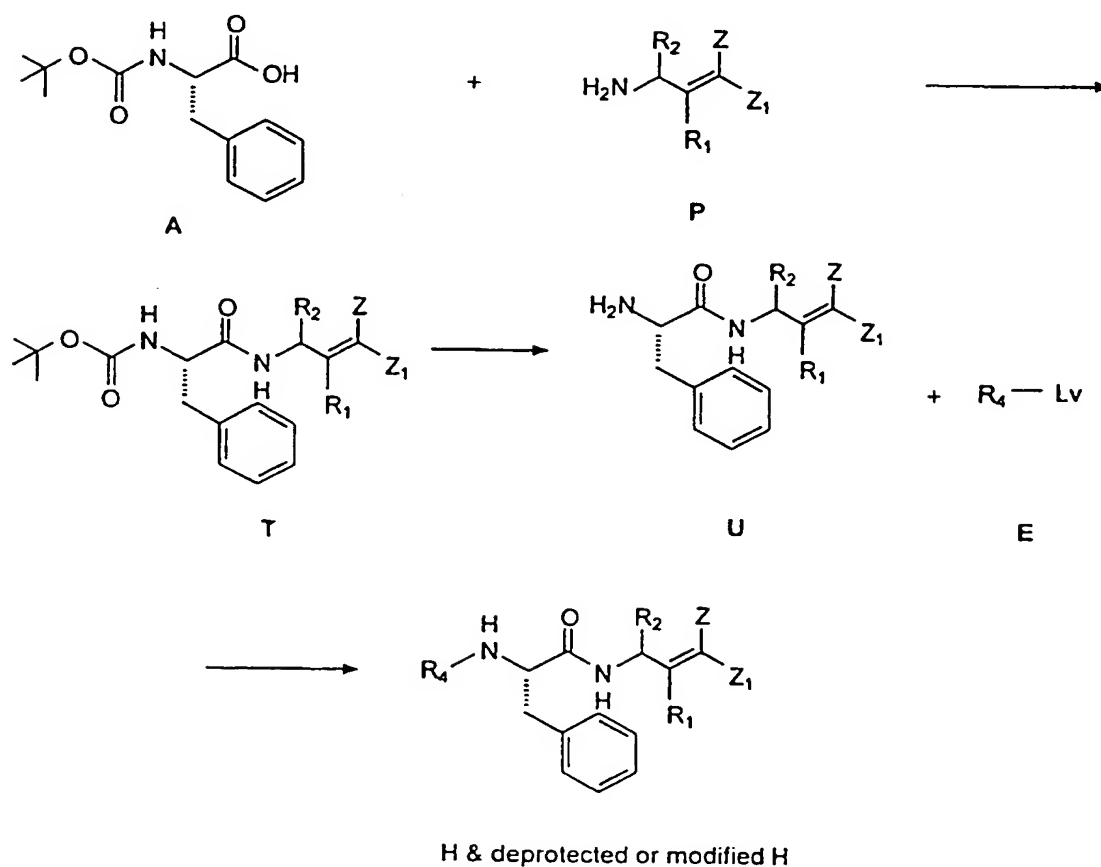
In Specific Method II, intermediate P (or salt thereof), prepared as described in General Method II, is subjected to an amide forming reaction with carboxylic acid K, CBZ-L-Leu-L-Phe, which can be purchased from Bachem or prepared as described in General Method I, to give final product H. If protecting groups were used on any R group (R_1 - R_6) and/or on Z and/or Z_1 , product H is deprotected and/or further modified to yield "deprotected or modified H."

For example, compounds 5, 13, and 15 can be prepared by Specific Method III:



In Specific Method III, free amine (or salt thereof) R, prepared as described in General Method III, is subjected to an amide forming reaction with carboxylic acid K, CBZ-L-Leu-L-Phe, which can be purchased from Bachem or prepared as described in General Method I, to give intermediate S. Intermediate S is then either converted directly to carbonyl intermediate G, in the case of compounds 13 and 15, or reduced to alcohol F, which is then oxidized to intermediate G, in the case of compound 5. Intermediate G is subjected to a reaction to yield the unsaturated final product H. If protecting groups were used on any R groups (R_1 - R_6) and/or on Z and/or Z_1 , product H is deprotected and/or further modified to yield "deprotected or modified H."

For example, compounds 31-34 can be prepared by Specific Method IV:



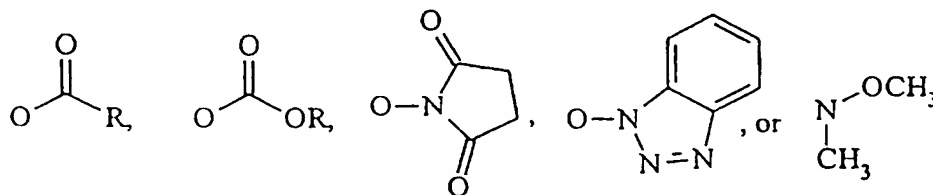
In Specific Method IV, free amine (or salt thereof) **P**, prepared as described in General Method II, is converted to amide **T** by reaction with protected amino acid **A**, which can be purchased from Bachem, Advanced Chemtech, and Synthetech. Compound **T** is further deprotected to free amine (or salt thereof) **U**, which is subsequently converted to **H** with reactive intermediate **E**. If protecting groups were used on any R groups (R_1 - R_4)

and/or on Z and/or Z₁, product H is deprotected and/or further modified to yield

"deprotected or modified H."

Suitable protecting groups for nitrogen are recognizable to those skilled in the art and include, but are not limited to benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, p-methoxybenzyloxycarbonyl, trifluoroacetamide, and p-toluenesulfonyl. Suitable protecting groups for oxygen are recognizable to those skilled in the art and include, but are not limited to -CH₃, -CH₂CH₃, tBu, -CH₂Ph, -CH₂CH=CH₂, -CH₂OCH₂CH₂Si(CH₃)₃, and -CH₂CCl₃. Other examples of suitable protecting groups for nitrogen or oxygen can be found in T. Green & P. Wuts, Protective Groups in Organic Synthesis (2nd ed. 1991), which is incorporated herein by reference.

Suitable leaving groups are recognizable to those skilled in the art and include, but are not limited to, Cl, Br, I, sulfonates, O-alkyl groups,



Other examples of suitable leaving groups are described in J. March, Advanced Organic Chemistry. Reactions, Mechanisms, and Structure (4th ed. 1992) at pages 205, 351-56, 642-43, 647, 652-53, 666, 501, 520-21, 569, 579-80, 992-94, 999-1000, 1005, and 1008, which are incorporated herein by reference.

EXAMPLES

Examples of the processes used to make several of the compounds of formulas I and II are set forth below. The structures of the compounds of the following Examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis, mass spectrometry, thin layer chromatography and melting point.

Proton magnetic resonance (NMR) spectra were determined using a Tech-Mag or Varian UNITYplus 300 spectrometer operating at a field strength of 300 megahertz (MHz). Chemical shifts are reported in parts per million (δ) and setting the references such that in CDCl₃, the CHCl₃ is at 7.26 ppm, in acetone-*d*₆ the acetone is at 2.02 ppm, and in DMSO-*d*₆ the DMSO is at 2.49 ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; bs, broad singlet; bt, broad triplet; m, multiplet. Mass spectra (FAB; fast atom bombardment) were determined at the Scripps Research Institute Mass Spectrometry Facility, San Diego, CA. Infrared absorption (IR) spectra were taken on a MIDAC Corporation FTIR or a Perkin-Elmer 1600 series FTIR spectrometer.

Elemental microanalysis were performed by Atlantic Microlab Inc. Norcross, Georgia and gave results for the elements stated with \pm 0.4% of the theoretical values. Flash chromatography was performed using Silica gel 60 (Merck Art 9385). Thin layer chromatographs (TLC) were performed on precoated sheets of silica 60 F₂₅₄ (Merck Art 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Anhydrous *N,N*-Dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA),

dimethylsulfoxide (DMSO), were used as is. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen.

Et₂O refers to diethyl ether. Pet. ether refers to petroleum ether having a boiling range of 36-53 °C. TFA refers to trifluoroacetic acid. Et₃N refers to triethylamine. Other abbreviations include: methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), acetyl (Ac), methyl (Me), phenyl (Phe), triphenylmethyl (Tr), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (BOC), *m*-chloroperoxybenzoic acid (*m*-CPBA), alanine (Ala), glutamine (Gln), leucine (Leu), methionine (Met), phenylalanine (Phe), penicillamine (Pen). Additionally, "L" represents natural amino acids, "D" represent unnatural amino acids, and "DL" represents racemic mixtures.

A simplified naming system was used to identify intermediates and final products. Amino acid and peptide alcohols are given the suffix 'ol' (for example methioninol). Amino acid and peptide aldehydes are given the suffix 'al' (for example methioninal). When naming final products, italicized amino acid abbreviations represent modifications at the C-terminus of that residue where the following apply:

1. acrylic acid esters are reported as either "E" (trans) or "Z" (cis) propenoates,
2. acrylonitriles are reported as either E or Z propenonitriles,
3. acrylamides are reported as either E or Z propenamides, except in the case of the compound 21, which is reported as 1-Pyrrolidin-1-yl-3-(CBZ-L-Leu-L-Phe-L-*Gln*)-E-Propenone,
4. vinyl sulfones, vinyl phosphonates, or vinyl aryls are reported as E or Z vinyl sulfones, vinyl phosphonates or aryls, and

5. vinyl ketones are reported as either E or Z en-2-ones.

Example 1 - Preparation of Compound 12: Ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)]-E-Propenoate

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-Methioninol

CBZ-L-Leu-L-Phe (3.02 g, 7.3 mmol) was dissolved in 75 mL of CH_2Cl_2 . To this solution was added N-hydroxysuccinimide (0.91 g, 7.7 mmol) and 2 mL of DMF, and stirring was continued until all solids had gone into solution. N,N'-Dicyclohexylcarbodiimide (1.60 g, 7.7 mmol) was added to the reaction mixture, and the reaction was stirred at room temperature for one hour. The mixture was then filtered into a separate flask containing S-(-)-methioninol (1.06 g, 7.7 mmol) dissolved in a minimum of DMF, removing the N,N'-dicyclohexylurea precipitate. The reaction was allowed to stir overnight at room temperature. The solvents were removed under vacuum, and the resulting crude product was purified by flash chromatography (anhydrous NH_3 / MeOH/ CHCl_3 , 0.5:4.5:9.5) on silica gel to give 3.72 g (96%) of white solid: IR (KBr) 3293, 3065, 2955, 1696, 1645, 1539, 1236, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.80 (m, 6 H), 1.31 (m, 2 H), 1.51 (m, 2 H), 1.82 (m, 1 H), 2.00 (s, 3 H), 2.43 (m, 2 H), 2.78-3.29 (m, 4 H), 3.72 (m, 1H), 3.97 (m, 1 H), 4.45 (m, 1 H), 4.66 (t, 1 H, $J = 5.5$ Hz), 5.01 (s, 2 H), 7.15-7.39 (m, 10 H), 7.43 (d, 1H, $J = 8.1$ Hz), 7.62 (d, 1 H, $J = 8.5$ Hz), 7.95 (d, 1 H, $J = 8.1$ Hz). Anal. ($\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_3\text{S}$) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-Methioninol (sulfoxide)

CBZ-L-Leu-L-Phe-L-methioninol (1.50 g, 2.80 mmol) was dissolved in 50 mL of CH_2Cl_2 . A total amount of 0.61 g (3.5 mmol) of *m*-CPBA was added portionwise over a period of five hours as the reaction was stirred at room temperature. After an additional hour, the reaction was poured into saturated $\text{NaHCO}_3/\text{CH}_2\text{Cl}_2$. The organic layer was separated, washed with brine, and dried (Na_2SO_4). After removal of the solvent, the crude residue was flash chromatographed on a short flash silica gel column eluting with 5% $\text{MeOH}/\text{CHCl}_3$. The product was obtained as a white glassy solid (1.38 g, 90%): IR (KBr) 3295, 3063, 2955, 1694, 1644, 1541, 1263, 1234, 1043, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.81 (m, 6 H), 1.32 (m, 2 H), 1.59 (m, 2 H), 1.92 (m, 1 H), 2.47 (s, 3 H), 2.55-3.29 (m, 6 H), 3.73 (m, 1 H), 3.97 (m, 1 H), 4.42 (m, 1 H), 4.75 (t, 1 H, $J = 5.5$ Hz), 5.01 (m, 2 H), 7.16-7.39 (m, 10 H), 7.44 (d, 1 H, $J = 7.7$ Hz), 7.73 (d, 1 H, $J = 8.8$ Hz), 7.98 (m, 1 H). Anal. ($\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_4\text{S}$) C, H, N, S.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-Methioninal (sulfoxide)

CBZ-L-Leu-L-Phe-L-methioninol (sulfoxide) (1.38 g, 2.53 mmol) was dissolved in DMSO. *o*-Iodoxybenzoic acid (2.12 g, 7.59 mmol) was added, requiring a few minutes of stirring at room temperature to dissolve. After three hours, the DMSO was removed under reduced pressure. The residue was twice diluted with CH_2Cl_2 , and the solvent was evaporated to remove any residual DMSO. The residue was diluted with a minimum of acetone, and the white precipitate was filtered off. The filtrate was concentrated to near dryness and dissolved in EtOAc, which produced more of the white precipitate, which was

again filtered off. The filtrate was washed with a 10% $\text{Na}_2\text{S}_2\text{O}_3$ /10% NaHCO_3 solution, water, and brine before drying over Na_2SO_4 . Upon removal of the organic solvent, the residue was twice taken up in benzene and evaporated to remove any residual water, giving 0.98 g (71%) of a white glassy solid which was used immediately without further purification: ^1H NMR ($\text{DMSO}-d_6$) δ 0.81 (m, 6H), 1.30 (m, 2H), 1.50 (m, 1H), 1.97 (m, 1H), 2.48 (s, 3H), 2.55-3.27 (m, 5H), 3.70 (m, 1H), 4.47 (m, 1H), 4.71 (m, 1H), 5.00 (s, 2H), 7.20-7.40 (m, 10H), 7.93 (m, 1H), 8.08 (m, 1H), 8.51 (m, 1H), 9.22 (s, 1H); (M+H) 544.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)]-E-Propenoate

CBZ-L-Leu-L-Phe-L-Methioninal (sulfoxide) (0.98 g, 1.80 mmol) was dissolved in 50 mL of THF. (Carbethoxymethylene)triphenyl-phosphorane (1.11 g, 2.16 mmol) was added, and the reaction was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue subjected to flash column chromatography eluting with 2% MeOH/ CHCl_3 . The product was obtained (0.82 g, 74%) as a white solid: ^1H NMR ($\text{DMSO}-d_6$) δ 0.81 (m, 6H), 1.21 (t, 3H, $J = 7$ Hz), 1.34 (m, 2H), 1.54 (m, 1H), 1.78 (m, 1H), 1.93 (m, 1H), 2.49 (s, 3H), 2.50-3.05 (m, 4H), 3.99 (m, 1H), 4.10 (q, 2H, $J = 7$ Hz), 4.51 (m, 2H), 5.00 (dd, 2H, $J = 17.3, 4.4$ Hz), 5.62 (m, 1H), 6.72 (m, 1H), 7.19 (m, 5H), 7.34 (m, 5H), 7.43 (d, 1H, $J = 8.1$ Hz), 8.08 (d, 1H, $J = 7.4$ Hz), 8.13 (d, 1H, $J = 8.5$ Hz); (M+H) 614; HRMS calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_5\text{S} + \text{Cs}$ 746.1876 (M+Cs), found 746.1850. Anal. ($\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_5\text{S}$) C, H, N, S.

Example 2 - Preparation of Compound 4: Ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-Ala]-E-Propenoate

Preparation of Intermediate CBZ-L-(N-Ac-amino)-Ala

CBZ-L-Amino-Ala (1.5 g, 6.3 mmol) was suspended in 50 mL of H₂O with stirring. Acetic anhydride (5.0 mL) was added slowly to this suspension over a 30 minute period, during which time the starting material dissolved. The reaction mixture was stirred for an additional 1 hour at room temperature and then evaporated to dryness under vacuum. The resulting oil was dissolved in 30 mL CHCl₃ and left for 12 hours. The solid that formed was collected by filtration, washed with 30 mL of CHCl₃ and dried yielding 1.29 g (73%) of product as a white solid: IR (KBr) 3271, 3125, 3065, 1734, 1703, 1614, 1545, 1289, 1244, 1053, 727 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.84 (s, 3H), 3.2-3.55 (m 2H), 4.13 (m, 1H), 5.08 (s, 2H), 7.12-7.41 (m, 5H), 7.54 (d, 1H, *J* = 8.1 Hz), 8.02 (bt, 1H, *J* = 5.5 Hz), 12.78 (bs, 1H); Anal. (C₁₇H₁₆N₂O₃) C, H, N.

Preparation of Intermediate CBZ-L-(N-Ac-amino)-Ala-OMe

Anhydrous HCl gas was slowly bubbled at 0 °C into a stirred suspension of CBZ-L-(N-Ac-amino)-Ala (1.21 g, 4.3 mmol) in MeOH (43 mL) until the solid was dissolved. Stirring was continued for 30 minutes at 0 °C whereupon the methanolic HCl was carefully evaporated to dryness. The methyl ester was formed as a white solid in quantitative yield and used without further purification: IR (KBr) 3323, 3285, 3094, 2957, 1755, 1736, 1686, 1651, 1531, 1277, 1057, 736, 600 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.78 (s, 3H), 3.22-3.47 (m,

2H), 3.61 (s, 3H), 4.15 (m, 1H), 5.02 (s, 2H), 7.24-7.36 (m, 5H), 7.64 (d, 1H, $J = 7.7$ Hz), 7.97 (bt, 1H, $J = 6.3$ Hz); Anal. ($C_{14}H_{11}N_2O_3$) C, H, N.

Preparation of Intermediate CBZ-L-(N-Ac-amino)-Alaninol

To a solution of CBZ-L-(N-Ac-amino)-Ala-OMe (1.8 g, 6.12 mmol) in 50 mL anhydrous THF/EtOH (2:1) was added LiCl (0.52 g, 12.24 mmol). Upon dissolution, NaBH₄ (0.46 g, 12.24 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was evaporated to near dryness, whereupon 45 mL of H₂O was added. The pH of this mixture was adjusted to 2-3 using concentrated HCl, followed by extraction with EtOAc (300 mL). The organic layer was washed with H₂O (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (10% MeOH/CHCl₃) to give 1.38 g (85%) of a white solid: IR (KBr) 3303, 3082, 2951, 2926, 1689, 1645, 1547, 1284, 1061, 1046, 756, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.78 (s, 3H), 3.03 (m, 1H), 3.16-3.28 (m, 3H), 3.49 (m, 1H), 5.00 (s, 2H), 6.95 (d, 1H, $J = 8.1$ Hz), 7.29-7.38 (m, 5H), 7.83 (bt, 1H, $J = 5.5$ Hz); Anal. ($C_{17}H_{19}N_2O_4$) C, H, N.

Preparation of Intermediate L-(N-Ac-amino)-Alaninol

To a solution of CBZ-L-(N-Ac-amino)-alaninol (1.36 g, 5.11 mmol) in 40 mL MeOH, 10% Pd on carbon (0.15 g) was added with stirring while under an argon atmosphere. The reaction vessel was evacuated under vacuum and then put under an atmosphere of hydrogen using a balloon. The mixture was stirred for 2 hours. At this time

the hydrogen gas was evacuated, and the catalyst was removed by filtration. The solvent was removed under vacuum. Addition of EtOAc and re-concentration gave a white hygroscopic solid in quantitative yield which was used without further purification: mp = 80-82 °C; ¹H NMR (DMSO-*d*₆) δ 1.79 (s, 3H), 2.66 (m, 1H), 2.86 (m, 1H), 3.06 (m, 1H), 3.21 (2H, m), 3.4 (bs, 2H), 4.55 (bs, 1H), 7.76 (bs, 1H). Anal. (C₁₁H₁₁N₂O₂) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-Alaninol

This compound was prepared from CBZ-L-Leu-L-Phe and L-(N-Ac-amino)-alaninol using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninol. The compound was purified by column chromatography (7% MeOH/CHCl₃) to give a white solid (81%): IR (KBr) 3302, 2955, 1694, 1651, 1539, 1454, 1236, 1047, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.80 (s, 6H), 1.32 (m, 2H), 1.47 (m, 1H), 1.79 (s, 3H), 2.81 (m, 1H), 2.97 (m, 2H), 3.14-3.25 (m, 3H), 3.71 (m, 1H), 3.95 (m, 1H), 4.42 (m, 1H), 4.67 (t, 1H, *J* = 5.5 Hz), 5.00 (m, 2H), 7.16-7.34 (m, 10H), 7.45 (d, 1H, *J* = 8.1 Hz), 7.70 (m, 2H), 7.88 (d, 1H, *J* = 8.1 Hz); Anal. (C₃₁H₃₁N₄O₆) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-Alaninal

This compound was prepared in 73% yield as a white solid from CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-alaninol using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninal (sulfoxide). The product was used immediately without further purification. The product existed as a mixture of aldehyde and aldehyde hydrate. IR (KBr) 3294, 2957, 1695, 1649, 1539, 1263, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.81(dd,

6H, $J = 8.8, 6.2$ Hz), 1.31 (m, 2H), 1.50 (m, 1H), 1.76 (s, hydrate), 1.78 (s, 3H), 2.83 (m, 1H), 3.00 (m, 1H), 3.20 (d, $J = 9.6$ Hz, hydrate), 3.35 (m, 1H), 3.80 (m, hydrate), 3.97 (m, 2H), 4.16 (m, 1H), 4.37 (m, hydrate), 4.44 (m, hydrate), 4.54 (m, 1H), 5.01 (s, 2H), 6.28 (d, 1H, $J = 7.0$ Hz, hydrate), 6.41 (d, 1H, $J = 6.6$ Hz, hydrate), 7.12-7.50 (m, 10H), 7.63 (t, 1H, $J = 7.9$ Hz), 7.87 (m, 1H), 7.98 (d, 1H, $J = 8.1$ Hz), 8.40 (d, 1H, $J = 7.0$ Hz), 9.26 (s, 1H); Anal. ($C_{44}H_{46}N_4O_4 \cdot 0.5 H_2O$) C, H, N.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-Ala]-E-Propenoate

This compound was prepared in 55% yield as a white solid from CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-alaninal and (carbethoxymethylene)triphenylphosphorane using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate]. The product was purified by flash column chromatography (3% MeOH/ $CHCl_3$). 1H NMR ($DMSO-d_6$) δ 0.81 (dd, 6H, $J = 9.2, 6.6$ Hz), 1.21 (t, 3H, $J = 7.2$ Hz), 1.34 (m, 2H), 1.53 (m, 1H), 1.78 (s, 3H), 2.80-3.28 (m, 4H), 3.99 (m, 1H), 4.10 (q, 2H, $J = 7.0$ Hz), 4.43 (m, 2H), 5.01 (m, 2H), 5.61 (d, 1H, $J = 15.4$ Hz), 6.61 (dd, 1H, $J = 15.4, 5.2$ Hz), 7.10-7.34 (m, 10H), 7.44 (d, 1H, $J = 7.7$ Hz), 7.70 (m, 2H), 7.82 (t, 1H, $J = 5.5$ Hz), 8.05 (m, 2H); HRMS calcd for $C_{44}H_{46}N_4O_4 + Cs$ 727.2108 (M+Cs), found 727.2137. Anal. ($C_{44}H_{46}N_4O_4$) C, H, N.

Example 3 - Preparation of Compound 2: Ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate**Preparation of Intermediate BOC-L-(Tr-Gln)-N(Me)OMe**

Isobutyl chloroformate (0.611 mL, 4.71 mmol) was added to a solution of BOC-L-(Tr-Gln) (2.30 g, 4.71 mmol) and 4-methylmorpholine (1.04 mL, 9.46 mmol) in CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes then *N,O*-dimethylhydroxylamine hydrochloride (0.459 g, 4.71 mmol) was added. The resulting solution was stirred at 0 °C for 15 minutes and at 23 °C for 4 hours, then was partitioned between water (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The combined organic layers were dried over Na₂SO₄ and were concentrated. Purification of the residue by flash column chromatography (40% hexanes in EtOAc) afforded the product (2.22 g, 89%) as a white foam: *R*_f = 0.22 (50% EtOAc in hexanes); IR (KBr) 3411, 3329, 3062, 1701, 1659 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (s, 9H), 1.63-1.77 (m, 1H), 2.06-2.17 (m, 1H), 2.29-2.43 (m, 2H), 3.17 (s, 3H), 3.64 (s, 3H), 4.73 (bs, 1H), 5.38-5.41 (m, 1H), 7.20-7.31 (m, 15H); Anal. (C₃₁H₃₇N₃O₅) C, H, N.

Preparation of Intermediate BOC-L-(Tr-Glutaminal)

Diisobutylaluminum hydride (7.84 mL of 1.5 M solution in toluene, 11.76 mmol) was added to a solution of BOC-L-(Tr-Gln)-N(Me)OMe (2.50 g, 4.70 mmol) in THF at -78 °C, and the reaction mixture was stirred at -78 °C for 4 hours. Methanol (3 mL) and 1.0 M HCl (6 mL) were added sequentially, and the mixture was warmed to 23 °C. The resulting suspension was diluted with Et₂O (150 mL) and was washed with 1.0 M HCl (3 x

100 mL), half-saturated NaHCO_3 (100 mL), and water (100 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated to give crude aldehyde (2.01 g, 91%) as a white solid: mp = 114-116 °C; R_f = 0.42 (50% EtOAc in hexanes); IR (KBr) 3313, 1697, 1494 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.44 (s, 9H), 1.65-1.75 (m, 1H), 2.17-2.23 (m, 1H), 2.31-2.54 (m, 2H), 4.11 (bs, 1H), 5.38-5.40 (m, 1H), 7.11 (s, 1H), 7.16-7.36 (m, 15H), 9.45 (s, 1H).

Preparation of Intermediate Ethyl-3-[BOC-L-(Tr-Gln)]-E-Propenoate

Sodium bis(trimethylsilyl)amide (3.38 mL of a 1.0 M solution in THF, 3.3 mmol) was added to a solution of triethyl phosphonoacetate (0.732 mL, 3.39 mmol) in THF (100 mL) at -78 °C, and the resulting solution was stirred for 20 minutes at that temperature. BOC-L-(Tr-Glutaminal) (1.60 g, 3.39 mmol) in THF (20 mL) was added via cannula, and the reaction mixture was stirred for 4 hours at -78 °C then was partitioned between 1.0 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) provided ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (1.53 g, 83%) as a white foam: R_f = 0.60 (50% EtOAc in hexanes); IR (cm^{-1}) 3321, 1710; ^1H NMR (CDCl_3) δ 1.27 (t, 3 H, J = 7.2 Hz), 1.42 (s, 9H), 1.70-1.78 (m, 1H), 1.80-1.96 (m, 1H), 2.35 (t, 2H, J = 7.0 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.29 (bs, 1H), 4.82-4.84 (m, 1H), 5.88 (dd, 1H, J = 15.7, 1.6 Hz), 6.79 (dd, 1H, J = 15.7, 5.3 Hz), 6.92 (s, 1H), 7.19-7.34 (m, 15H); Anal. ($\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_6$) C, H, N.

Preparation of Product Ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate

Ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.224 g, 0.422 mmol) was dissolved in 1,4-dioxane (3 mL) and cooled to 0 °C. A solution of HCl in 1,4-dioxane (4.0 M, 3 mL, 12 mmol) was added dropwise, and the reaction solution was allowed to warm to room temperature. After being stirred for 2 hours, the solution was diluted with 1:1 CH₂Cl₂/EtOAc (50 mL) and added to a solution of NaOH (16 mmol) in saturated aqueous NaHCO₃ (50 mL). After vigorous shaking, the phases were separated, and the aqueous phase was washed 2 more times with 1:1 CH₂Cl₂/EtOAc (50 mL). The combined organic phases were dried over Na₂SO₄ and concentrated to give 0.164 g (88%) of the crude free amine, which was used without further purification.

The crude amine (0.371 mmol, 1.0 equiv) was dissolved in dry CH₂Cl₂ (5 mL). CBZ-L-Leu-L-Phe (0.176 g, 0.427 mmol), 1-hydroxybenzotriazole hydrate (0.081 g, 0.599 mmol), 4-methylmorpholine (0.175 mL, 1.59 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.114 g, 0.595 mmol) were added sequentially. After being stirred for 18 hours at 23 °C, the reaction mixture was poured into water (40 mL) and extracted with 1:1 CH₂Cl₂/EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and were concentrated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to give the product (0.163 g, 49%) as a white solid: mp = 192-194 °C; IR (KBr) 3295, 3049, 1696, 1654 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (d, 3H, *J* = 6.5 Hz), 0.86 (d, 3H, *J* = 6.5 Hz), 1.24-1.32 (m, 1H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.43-1.75 (m, 3H), 1.91-2.06 (m, 1H), 2.20-2.38 (m, 2H), 2.93-3.02 (m, 1H), 3.07-3.18 (m, 1H), 3.95-4.02 (m, 1H), 4.17 (q, 2H, *J* = 7.2 Hz), 1.43-4.55 (m, 2H), 4.82-4.95 (m, 2H),

5.69 (d, 1H, $J = 15.7$ Hz), 6.46 (d, 1H, $J = 7.5$ Hz), 6.60 (d, 1H, $J = 8.1$ Hz), 6.69 (dd, 1H, $J = 15.7, 5.1$ Hz), 7.09-7.38 (m, 27 H); Anal. ($C_{31}H_{36}N_4O_7$) C, H, N.

Example 4 - Preparation of Compound 3: Ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Preparation of Product - Ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Compound 2, ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.15 g, 0.18 mmol), prepared as described in Example 3, was dissolved in 1:1 CH_2Cl_2 /TFA (5 mL) at 23 °C and the bright yellow solution was stirred 30 minutes, whereupon the solvent was evaporated. CCl_4 (10 mL) was added, and the resulting solution was concentrated twice. Addition of Et_2O (10 mL) to the oily residue quickly gave a white precipitate. After stirring 10 minutes, the solid was collected by filtration and washed sequentially with acetone (2 x 10 mL) and Et_2O (2 x 10 mL) then was dried *in vacuo* to give ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate (0.057 mg, 53%) as a white solid: mp = 219-221 °C; IR (KBr) 3300, 3065, 1672 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 0.78 (d, 3H, $J = 6.8$ Hz), 0.82 (d, 3H, $J = 6.5$ Hz), 1.21 (t, 3H, $J = 7.0$ Hz), 1.25-1.37 (m, 2H), 1.42-1.54 (m, 1H), 1.58-1.80 (m, 2H), 2.02-2.09 (m, 2H), 2.84 (dd, 1H, $J = 13.2, 8.9$ Hz), 2.97 (dd, 1H, $J = 13.2, 5.8$ Hz), 3.93-4.01 (m, 1H), 4.11 (q, 2H, $J = 7.0$ Hz), 4.33-4.52 (m, 2H), 4.97 (d, 1H, $J = 12.3$ Hz), 5.04 (d, 1H, $J = 12.3$ Hz), 5.64 (d, 1H, $J = 15.9$ Hz), 6.69 (dd, 1H, $J = 15.9, 5.4$ Hz), 6.76 (s, 1H), 7.13-7.37 (m, 11H), 7.43 (d, 1H, $J = 7.8$ Hz), 7.99 (d, 1H, $J = 8.1$ Hz), 8.04 (d, 1H, $J = 8.1$ Hz); Anal. ($C_{33}H_{42}N_4O_7$) C, H, N.

Example 5 - Preparation of Compound 7: Methyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-Z-Propenoate**Preparation of Intermediate Methyl-3-[BOC-L-(Tr-Gln)]-Z-Propenoate**

18-crown-6 (0.867 g, 3.28 mmol) was evaporated from toluene (40 mL) and then dissolved in dry THF (14 mL) under argon. Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.111 mL, 0.525 mmol) was added, and the reaction mixture was cooled to -78 °C. After dropwise addition of a solution of potassium bis(trimethylsilyl)amide in toluene (0.5 M, 1.26 mL, 0.63 mmol), the reaction mixture was stirred for 25 minutes. A solution of BOC-L-(Tr-glutaminal) (0.310 g, 0.656 mmol) in dry THF (4 mL) was added dropwise, and, after stirring 1 hour more, saturated aqueous NH₄Cl (2 mL) was added. The reaction mixture was allowed to warm to room temperature, and the THF was evaporated. Water (10 mL) was added to the residue, which was then extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (35% EtOAc/hexanes) to give the product (0.181 g, 52%) as a glass: IR (thin film) 3326, 1713, 1690, 1666, 1514 cm⁻¹; ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 1.84-1.93 (m, 2H), 2.37-2.44 (m, 2H), 3.68 (s, 3H), 5.10 (m, 2H), 5.80 (d, 1H, *J* = 11.8 Hz), 6.03 (m, 1H), 6.88 (bs, 1H), 7.18-7.32 (m, 15H).

Preparation of Intermediate Methyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-Z-Propenoate

Methyl-3-[BOC-L-(Tr-Gln)]-Z-propenoate (0.143 g, 0.271 mmol) was dissolved in 1,4-dioxane (3 mL) at room temperature. A solution of HCl in 1,4-dioxane (4.0 M, 3 mL)

was added dropwise, and the reaction solution was stirred for 2 hours under an argon balloon. Then the solvent was evaporated to give the crude amine salt as a glassy residue, which was used without further purification. This amine salt, CBZ-L-Leu-L-Phe (0.112 g, 0.272 mmol), and 1-hydroxybenzotriazole hydrate (0.055 g, 0.40 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under argon at room temperature. 4-Methylmorpholine (0.149 mL, 1.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.078 g, 0.40 mmol) were then added sequentially. After stirring for 3 hours, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (33% acetone in hexanes) to give the product (0.132 g, 59%) as a white foam: IR (thin film) 3296, 1708, 1650, 1517 cm^{-1} ; Anal. ($\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_7$) C, H, N.

Preparation of Product - Methyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-Z-Propenoate

Methyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-Z-propenoate (0.110 g, 0.134 mmol) was dissolved in 1:1 CH_2Cl_2 /TFA (4 mL), giving a bright yellow solution, which was stirred for 30 minutes under an argon balloon. CCl_4 (7 mL) was added, and the solution was concentrated twice. The residue was triturated with Et_2O (3 mL) to give a white solid, which was collected by filtration and dried *in vacuo* (0.040 g, 51%): mp = 185-188 °C; IR (KBr) 3401, 3283, 1719, 1690, 1643, 1538 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.78 (d, 3H, $J = 6.6$ Hz), 0.82 (d, 3H, $J = 6.5$ Hz), 1.22-1.38 (m, 2H), 1.43-1.54 (m, 1H), 1.58-1.75 (m, 2H), 1.92-2.09 (m, 2H), 2.77-2.90 (m, 2H), 3.65 (s, 3H), 3.91-4.00 (m, 1H), 4.37-4.46 (m, 1H), 4.99 (d, 1H, $J = 12.6$ Hz), 5.04 (d, 1H, $J = 12.6$ Hz), 5.18-5.25 (m, 1H), 5.79 (d, 1H, $J = 11.5$

Hz), 5.92 (dd, 1H, $J = 11.5, 8.7$ Hz), 6.72 (s, 1H), 7.14-7.36 (m, 11H), 7.43 (d, 1H, $J = 8.0$ Hz), 7.76 (d, 1H, $J = 8.1$ Hz), 8.01 (d, 1H, $J = 8.0$ Hz); Anal. ($C_{31}H_{40}N_4O_7$) C, H, N.

Example 6 - Preparation of Compound 11: Methyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Preparation of Intermediate Methyl-3-[BOC-L-(Tr-Gln)]-E-Propenoate

Sodium bis(trimethylsilyl)amide (0.978 mL of a 1.0 M solution in THF, 0.978 mmol) was added to a solution of trimethyl phosphonoacetate (0.144 mL, 0.890 mmol) in THF (20 mL) at -78°C , and the resulting solution was stirred for 15 minutes at that temperature. BOC-L-(Tr-Glutaminal) (0.420 g, 0.889 mmol) in THF (10 mL) was added via cannula, and the reaction mixture was stirred for 2 hours at -78°C , then was partitioned between 0.5 M HCl (100 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 100 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution, 30-40% EtOAc in hexanes) provided methyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.460 g, 96%) as a white solid: mp $110-112^\circ\text{C}$; IR (thin film) 3318, 1708, 1665 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.42 (s, 9H), 1.72-1.82 (m, 1H), 1.91-1.98 (m, 1H), 2.34-2.41 (m, 2H), 3.72 (s, 3H), 4.29 (s, br, 1H), 4.78-4.81 (m, 1H), 5.89 (dd, 1H, $J = 15.6, 1.6$ Hz), 6.80 (dd, 1H, $J = 15.6, 5.3$ Hz), 6.87 (s, 1H), 7.19-7.33 (m, 15H).

Preparation of Intermediate Methyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 28 for the preparation of ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, methyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.157 g, 0.297 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.123 g, 0.298 mmol) to provide methyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.176 g, 72%) as a white foam: ^1H NMR (CDCl_3) δ 0.84 (d, 3H, $J = 6.7$ Hz), 0.86 (d, 3H, $J = 6.7$ Hz), 1.45-1.61 (m, 3H), 1.67-1.75 (m, 1H), 1.94-1.96 (m, 1H), 2.20-2.35 (m, 2H), 2.95-3.15 (m, 2H), 3.72 (s, 3H), 3.94-4.01 (m, 1H), 4.46-4.49 (m, 1H), 4.83-4.93 (m, 3H), 5.72 (d, 1H, $J = 15.8$ Hz), 6.45 (d, 1H, $J = 7.2$ Hz), 6.63 (d, 1H, $J = 8.1$ Hz), 6.71 (dd, 1H, $J = 15.8, 5.1$ Hz), 7.01-7.38 (m, 27H).

Preparation of Product - Methyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, methyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.087 g, 0.106 mmol) was deprotected to provide methyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate (0.015 g, 25%) as a white solid: mp = 220 °C (dec); ^1H NMR ($\text{DMSO}-d_6$) δ 0.79 (d, 3H, $J = 10.9$ Hz), 0.81 (d, 3H, $J = 10.9$ Hz), 1.26-1.34 (m, 2H), 1.47-1.49 (m, 1H), 1.61-1.76 (m, 2H), 2.06 (t, 2H, $J = 7.6$ Hz), 2.84 (dd, 1H, $J = 13.5, 9.0$ Hz), 2.97 (dd, 1H, $J = 13.5, 5.6$ Hz), 3.65 (s, 3H), 3.93-3.97 (m, 1H), 4.38 (s, br, 1H), 4.44-4.49 (m, 1H), 4.97 (d, 1H, $J = 12.5$ Hz), 5.04 (d, 1H, $J = 12.5$ Hz), 5.68 (d, 1H, $J = 15.6$ Hz), 6.70 (dd, 1H, $J = 15.6, 5.5$ Hz), 6.76 (s, 1H), 7.19 (s, br, 7H), 7.34 (s, br, 4H), 7.44 (d, 1H, $J = 7.5$ Hz), 7.99 (d, 1H, $J = 8.1$ Hz), 8.05 (d, 1H, $J = 8.1$ Hz).

Example 7 - Preparation of Compound 13: 4-(CBZ-L-Leu-L-Phe-L-Gln)-E-3-Butene-2-one

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(Tr-Gln)-N(Me)OMe

BOC-L-(Tr-Gln)-N(Me)OMe (0.807 g, 1.52 mmol) was dissolved in 1,4-dioxane (4.5 mL) at room temperature. A solution of HCl in 1,4-dioxane (4.0 M, 4.5 mL) was added dropwise, and the reaction solution was stirred for 2.5 hours under an argon balloon. The solvent was evaporated to give the crude amine salt as a white foam, which was used without further purification. This amine salt, CBZ-L-Leu-L-Phe (0.626 g, 1.52 mmol) and 1-hydroxybenzotriazole hydrate (0.308 g, 2.28 mmol) were stirred in dry CH₂Cl₂ (12 mL) under argon at room temperature. 4-Methylmorpholine (0.840 mL, 7.64 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.436 g, 2.27 mmol) were added sequentially. After stirring for 3 hours, the reaction solution was poured into water (25 mL), and the aqueous layer was extracted 3 times with CH₂Cl₂ (70 mL, 40 mL, and 30 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (40% acetone in hexanes) to give the product (0.826 g, 66%) as a white foam: IR (thin film) 3300, 1643, 1525 cm⁻¹.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(Tr-Glutaminal)

CBZ-L-Leu-L-Phe-L-(Tr-Gln)-N(Me)OMe (0.768 g, 0.930 mmol) was dissolved in dry THF (12 mL) under argon and cooled to -78 °C. A solution of diisobutylaluminum hydride in toluene (1.5 M, 2.17 mL, 3.26 mmol) was added dropwise. After stirring 3

hours, methanol (0.7 mL) was added slowly, followed by 1 N HCl (1 mL). The reaction mixture was allowed to warm to nearly room temperature and was then diluted with 5:1 CH₂Cl₂/EtOAc (120 mL). The resulting mixture was washed with 1 N HCl (2 x 15 mL), half-saturated NaHCO₃ (15 mL) and brine (25 mL). The organic phase was dried over MgSO₄ and concentrated to give the product as an off-white foam (0.606 g, 85%), which was used without further purification. An analytical sample was purified by column chromatography (36% acetone in hexanes): IR (thin film) 3295, 1708, 1660, 1531 cm⁻¹; ¹H NMR (CDCl₃) δ 0.80 (d, 3H, *J* = 6.2 Hz), 0.87 (d, 3H, *J* = 6.4 Hz), 1.27-1.59 (m, 3H), 1.71-1.83 (m, 1H), 2.07-2.15 (m, 1H), 2.22-2.29 (m, 2H), 2.96 (dd, 1H, *J* = 13.7, 7.4 Hz), 3.08 (dd, 1H, *J* = 13.7, 6.2 Hz), 3.99-4.08 (m, 1H), 4.11-4.20 (m, 1H), 4.55-4.64 (m, 1H), 4.92 (bs, 2H), 5.17 (d, 1H, *J* = 6.7 Hz), 6.70 (d, 1H, *J* = 7.4 Hz), 7.08-7.35 (m, 27H), 9.26 (s, 1H); Anal. (C₄₇H₅₀N₄O₆) C, H, N.

Preparation of Intermediate 4-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-3-Butene-2-one

CBZ-L-Leu-L-Phe-L-(Tr-Glutaminal) (0.605 g, 0.789 mmol) and 1-triphenylphosphoranylidene-2-propanone (0.251 g, 0.788 mmol) were stirred in dry THF (7 mL) at room temperature, under argon, giving a yellow solution. After stirring 20 hours, the solvent was evaporated, and the residue was purified by flash column chromatography (36% acetone in hexanes) to give the product (0.425 g, 67%) as a white foam: IR (thin film) 3299, 1666, 1519 cm⁻¹.

Preparation of Product - 4-(CBZ-L-Leu-L-Phe-L-Gln)-E-3-Butene-2-one

This compound was prepared in 54% yield from 4-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-3-butene-2-one using the procedure described in Example 26 for the preparation of compound 14, 3-(CBZ-L-Leu-L-Phe-DL-Gln)-E-propenonitrile: mp = 194-196 °C (dec); IR (KBr) 3413, 3284, 1684, 1643, 1537 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.79 (d, 3H, $J = 6.6$ Hz), 0.82 (d, 3H, $J = 6.6$ Hz), 1.23-1.39 (m, 2H), 1.44-1.55 (m, 1H), 1.60-1.84 (m, 2H), 2.05-2.12 (m, 2H), 2.17 (s, 3H), 2.84 (dd, 1H, $J = 13.6, 8.7$ Hz), 2.99 (dd, 1H, $J = 13.6, 5.7$ Hz), 3.93-4.02 (m, 1H), 4.34-4.44 (m, 1H), 4.46-4.55 (m, 1H), 4.98 (d, 1H, $J = 12.6$ Hz), 5.04 (d, 1H, $J = 12.6$ Hz), 5.84 (d, 1H, $J = 16.0$ Hz), 6.64 (dd, 1H, $J = 16.0, 5.4$ Hz), 6.77 (s, 1H), 7.15-7.37 (m, 11H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.99 (d, 1H, $J = 8.1$ Hz), 8.06 (d, 1H, $J = 8.1$ Hz); Anal. ($\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_6$) C, H, N.

Example 8 - Preparation of Compound 5: Ethyl-3-[CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Ala]-E-Propenoate**Preparation of Intermediate CBZ-L-[N-(4-Chlorobutyl)-amino]-Ala-OMe**

Acetyl chloride (19.6 g, 250 mmol) was slowly added to a solution of MeOH (300 mL) at 0 °C. After 10 minutes, CBZ-L-amino-Ala (10 g., 42 mmol) was added, and the reaction was allowed to stir for 12 hours at room temperature. Removal of solvent under vacuum provided 13.5 g of crude CBZ-L-amino-Ala-OMe as the hydrochloride salt. The crude ester was taken up in 200 mL CH_2Cl_2 , to which was added Et₃N (10.6 g, 105 mmol) and then 4-chlorobutyl chloride (7.1 g, 50.4 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 4 hours. At this time the reaction mixture

was added to brine. The organic layer was extracted, washed with 1 N HCl, brine, dried over MgSO_4 , and concentrated yielding 19 g of crude material. The material was purified by flash column chromatography (50% EtOAc-hexanes), giving an 87% yield of product. ^1H NMR (CDCl_3) δ 2.07 (m, 2H), 2.35 (t, 2H, $J = 7.0$ Hz), 3.57 (t, 2H, $J = 6.3$ Hz), 3.67 (t, 2H, $J = 5.9$ Hz), 3.77 (s, 3H), 4.45 (m, 1H), 5.12 (s, 2H), 5.84 (d, 1H, $J = 6.3$ Hz), 6.00 (bs, 1H), 7.37 (s, 5H).

Preparation of Intermediate CBZ-L-[N-(2-pyrrolidinone)]-Ala-OMe

A solution of CBZ-L-[N-(4-chlorobutyl)-amino]-Ala-OMe (14.6 g, 39 mmol) in DMF (400 mL) was cooled to 0 °C. To the solution was added NaH (1.87 g of a 60% dispersion in oil, 46.8 mmol), and the mixture was stirred at room temperature for 4 hours. The DMF was removed under high vacuum, and the residue was taken up in EtOAc, washed with 1 N HCl, saturated aqueous NaHCO_3 , brine, dried over MgSO_4 , and concentrated. The material was purified by flash column chromatography (100% EtOAc), giving 7.0 g (56%) of product. ^1H NMR δ (CDCl_3) 1.97 (m, 2H), 2.35 (m, 2H), 3.36 (m, 1H), 3.40-3.60 (m, 3H), 3.77 (s, 3H), 4.52 (m, 1H), 5.13 (d, 2H, $J = 5.6$ Hz), 5.83 (d, 1H, $J = 6.3$ Hz), 7.37 (m, 5H).

Preparation of Intermediate L-[N-(2-pyrrolidinone)]-Ala-OMeHCl

This compound was prepared from CBZ-L-[N-(2-pyrrolidinone)]-Ala-OMe by catalytic hydrogenation as described in Example 2 for the preparation of L-(N-Ac-amino)-alaninol, except methanolic HCl was used in order to isolate the product as the HCl salt. ^1H

NMR (CDCl₃), δ 2.03 (m, 2H), 2.39 (m, 2H), 3.14 (bs, 2H), 3.40-3.70 (m, 5H), 3.75 (s, 3H).

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Ala-OMe

This compound was prepared from CBZ-L-Leu-L-Phe and L-[N-(2-pyrrolidinone)]-Ala-OMeHCl using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninol. ¹H NMR (CDCl₃), δ 0.89 (m, 6H), 1.36 (m, 2H), 1.56 (m, 1H), 1.61 (m, 2H), 2.04 (m, 3H), 2.31 (m, 2H), 3.07-3.70 (m, 6H), 3.75 (s, 3H), 4.11 (m, 1H), 4.71 (m, 1H), 5.13 (bs, 1H), 5.18 (bs, 1H), 6.76-6.88 (m, rotomers, 1H), 7.10-7.45 (m, 10H).

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Alaninol

This compound was prepared by the reduction of CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Ala-OMe with NaBH₄ and LiCl using the procedure described in Example 2 for the preparation of CBZ-L-(N-Ac-amino)-alaninol.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Alaninal

This compound was prepared from CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-alaninol using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninal (sulfoxide). Anal. (C₃₆H₄₁N₄O₆·1.4 H₂O) C, H, N.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-Ala]-E-Propenoate

This compound was prepared from CBZ-L-Leu-L-Phe-L-[N-(2-pyrrolidinone)]-alaninal and (carbethoxymethylene)triphenylphosphorane using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate. ¹H NMR (DMSO-*d*₆) δ 0.80 (d, 6H, *J*=7.0 Hz), 0.95-1.40 (m, 7H), 1.49 (m, 1H), 1.82 (m, 2H), 2.12 (m, 2H), 2.60-3.10 (m, 2H), 3.20 (m, 2H), 3.81 (m, 1H), 4.00 (m, 1H), 4.10 (m, 2H), 4.49 (m, 1H), 4.72 (m, 1H), 5.01 (bs, 1H), 5.70 (d, 0.5H -rotomer- *J* = 16.5 Hz), 5.97 (d, 0.5H -rotomer- *J* = 16.5 Hz), 6.70 (d, 0.5H -rotomer- *J* = 16.5 Hz), 6.80 (d, 0.5H -rotomer- *J* = 16.5 Hz), 7.20 (d, 2H, *J* = 7.4 Hz), 7.34 (m, 3H), 7.60 (m, 5H), 8.04 (m, 1H), 8.23 (m, 1H). HRMS calcd for C₃₄H₄₄N₄O₇+Cs 753.2264 (M + Cs), found 753.2295.

Example 9 - Preparation of Compound 16: Ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-carbamyl-amino)-Ala]-E-Propenoate**Preparation of Intermediate CBZ-L-(N-BOC-amino)-Ala**

To a stirred solution of NaOH (1.23 g, 30.76 mmol) in 36 mL of H₂O and 24 mL *tert*-butanol was added CBZ-L-amino-Ala (7.15 g, 30 mmol). To this solution was added di-*tert*-butyl dicarbonate (6.88 g, 31.5 mmol). Stirring was continued at room temperature for 12 hours, at which time the solution was washed with pet. ether (2 x 150 mL). The organic layers were washed with saturated aqueous NaHCO₃ (3 x 20 mL), and the aqueous layers were combined and acidified at 0 °C with 25% aqueous KHSO₄ to pH 2-3. This milky white mixture was then extracted with a large excess of Et₂O, dried over anhydrous

Na_2SO_4 , and concentrated to yield 9.13 g (90%) of product as a white solid, which was used without further purification. ^1H NMR ($\text{DMSO}-d_6$) δ 1.35 (s, 9H), 3.21 (m, 2H), 4.05 (m, 1H), 5.02 (s, 2H), 6.83 (bt, 1H, $J = 6.6$ Hz), 7.34 (m, 5H), 7.41 (d, 1H, $J = 8.1$ Hz), 12.65 (bs, 1H). This compound was further characterized as its corresponding methyl ester.

Preparation of Intermediate CBZ-L-(N-BOC-amino)-Ala-OMe.

A solution of diazomethane in Et_2O , generated from N-methyl-N-nitroso-p-toluenesulfonamide (7.7 g, 36.0 mmol), 70 mL Et_2O , 16 mL EtOH, 12 mL H_2O and KOH (7.65 g, 13.6 mmol) was carefully distilled into a stirred solution of CBZ-L-(N-BOC-amino)-Ala (7.8 g, 23.0 mmol) in 50 mL Et_2O and 10 mL EtOH at 0 °C. The yellow solution was stirred for 30 minutes. The cold solution was then brought to room temperature, and argon was bubbled into the reaction flask to remove any excess diazomethane. After the solution turned colorless, it was concentrated to give the methyl ester as a white solid in quantitative yield. mp = 72-74 °C; IR (KBr) 3418, 3331, 3005, 2955, 1753, 1724, 1676, 1552, 1525, 1298, 1045, 699 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.41 (s, 9H), 3.55 (m, 2H), 3.76 (s, 3H), 4.40 (m, 2H), 4.82 (m, 1H), 5.11 (s, 2H), 5.77 (m, 1H), 7.35 (m, 5H). Anal. ($\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_6$) C, H, N.

Preparation of Intermediate CBZ-L-(N-BOC-amino)-Alaninol

Using the borohydride reduction procedure described in Example 2 for the preparation of CBZ-L-(N-Ac-amino)-alaninol, CBZ-L-(N-BOC-amino)-Ala-OMe was converted to the corresponding alcohol and isolated in 96% yield without column

chromatography purification. mp = 116-119 °C; IR (KBr) 3327, 3277, 3065, 2976, 1699, 1682, 1543, 1315, 1250, 1062, 1001, 696 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.35 (s, 9H), 2.90-3.10 (m, 4H), 3.55 (m 1H), 4.60 (bt, 1H, *J* = 5.5 Hz), 4.99 (s, 2H), 6.72 (bt, 1H, *J* = 5.5 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 7.34 (m, 5H). Anal. (C₁₆H₁₄N₂O₃) C, H, N.

Preparation of Intermediate L-(N-BOC-amino)-Alaninol

Using the hydrogenation procedure described in Example 2 for the preparation of L-(N-Ac-amino)-alaninol, the CBZ group was removed from CBZ-L-(N-BOC-amino)-alaninol to give the amino alcohol in 98% yield. mp = 61-64 °C; IR (KBr) 3362, 2980, 2935, 1680, 1534, 1370, 1287, 1175, 1059, 642 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.36 (s, 9H), 2.64 (m, 1H), 2.72 (m, 1H), 2.93 (m, 1H), 3.13 (m, 1H), 3.32 (m, 2H), 4.45 (bs, 1H), 6.67 (bs, 1H); Anal. (C₈H₁₁N₂O₃) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-Alaninol

This compound was prepared from L-(N-BOC-amino)-alaninol and CBZ-L-Leu-L-Phe using the coupling procedure described in Example 2 for the preparation of CBZ-L-Leu-L-Phe-L-(N-Ac-amino)-alaninol. The reaction mixture was purified by flash column chromatography (5% saturated anhydrous NH₃ in MeOH/CH₂Cl₂) to give a white solid in 90% yield. IR (KBr) 3420, 3327, 3289, 3032, 2953, 1694, 1643, 1535, 1284, 1036, 696 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.80 (dd, 6H, *J* = 11.2, 6.4 Hz), 1.35 (s, 9H), 1.55 (m 2H), 1.72 (m, 1H), 2.89 (m, 2H), 3.19 (m, 2H), 3.78 (m, 1H), 3.92 (m, 1H), 4.44 (m, 1H), 4.62 (t, 1H, *J* = 5.5 Hz), 5.01 (d, 2H, *J* = 5.9 Hz), 6.63 (bt, 1H, *J* = 5.5 Hz), 7.18 (m, 5H), 7.34 (m, 5H),

7.45 (d, 1H, $J = 8.1$ Hz), 7.60 (d, 1H, $J = 7.7$ Hz), 7.85 (d, 1H, $J = 8.1$ Hz). Anal.

(C₃₁H₄₄N₄O₇) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-Alaninal

This compound was prepared in 90% yield as a white solid from CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-alaninol using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninal (sulfoxide). The product was used immediately without further purification. The product existed as a mixture of aldehyde and aldehyde hydrate. IR (KBr) 3299, 3067, 2959, 2934, 1696, 1647, 1535, 1254, 1171, 747, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.80 (dd, 6H, $J = 9.0, 6.8$ Hz), 1.35 (s, 9H), 1.41 (m, 2H), 1.69 (m, 1H), 2.80-3.01 (m, 2H), 3.29 (m, 2H), 3.97 (m, 1H), 4.10 (m, 1H), 4.60 (m, 1H), 5.00 (s, 2H), 5.56 (d, $J = 7.4$ Hz, hydrate), 6.78 (t, 1H, $J = 6.3$ Hz), 7.20 (m, 5H), 7.33 (m, 5H), 7.40 (d, 1H, $J = 8.1$ Hz), 7.97 (d, 1H, $J = 8.1$ Hz), 8.39 (d, 1H, $J = 6.6$ Hz), 9.26 (s, 1H); HRMS calcd for C₃₁H₄₄N₄O₇+Cs 715.2108 (M+Cs), found 715.2133. Anal. (C₃₁H₄₄N₄O₇·0.5 H₂O) C, H, N.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-Ala]-E-Propenoate

This compound was prepared in approximately 40% yield as a white foaming solid from CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-alaninal and (carbethoxymethylene)-triphenylphosphorane using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate. The product

was partially purified (impure with triphenylphosphine oxide as determined by NMR) by flash column chromatography (4% MeOH/CH₂Cl₂). ¹H NMR (DMSO-*d*₆) δ 0.80 (dd, 6H, *J* = 9.6, 6.3 Hz), 1.19 (t, 3H, *J* = 6.8 Hz), 1.34 (s, 9H), 1.45-1.70 (m, 3H), 2.82-3.05 (m, 4H), 3.99 (m, 1H), 4.08 (q, 2H, *J* = 7.0 Hz), 4.46 (m, 2H), 5.01 (m, 2H), 5.64 (d, 1H, *J* = 16.2 Hz), 6.61 (dd, 1H, *J* = 16.2, 5.5 Hz), 6.85 (bt, 1H, *J* = 5.2 Hz), 7.18 (m, 5H), 7.34 (m, 5H), 7.42 (d, 1H, *J* = 5.5 Hz), 7.96 (d, 1H, *J* = 7.4 Hz), 8.01 (d, 1H, *J* = 7.4 Hz); HRMS calcd for C₂₇H₃₄N₄O₄+Na 675.3370 (M+Na), found 675.3363.

Preparation of Intermediate Ethyl-3-(CBZ-L-Leu-L-Phe-L-amino-Ala)-E-Propenoate

To a stirred solution of ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-BOC-amino)-Ala]-E-propenoate (0.14 g, 0.215 mmol) in 12 mL CH₂Cl₂, cooled to 0 °C, was added 0.65 mL TFA dropwise. The reaction was followed by TLC (silica, 10% MeOH/CH₂Cl₂) until there was a disappearance of starting material. At this time the reaction mixture was taken up in 100 mL EtOAc and washed with saturated NaHCO₃ (3 x 10 mL). The organic layer was then washed with H₂O then saturated brine and dried over anhydrous Na₂SO₄. Concentration of the solution gave a residue, which was purified by flash column chromatography (8% MeOH/CH₂Cl₂) to give a beige foam in 84% yield. ¹H NMR (DMSO-*d*₆) δ 0.80 (dd, 6H, *J* = 9.4, 6.8 Hz), 1.22 (t, 3H, *J* = 7.2 Hz), 1.31 (m, 2H), 1.51 (m, 1H), 2.64 (m, 2H), 2.91 (m, 2H), 3.99 (m, 1H), 4.10 (q, 2H, *J* = 7.4 Hz), 4.36 (m, 1H), 4.49 (m, 1H), 5.02 (m, 2H), 5.60 (d, 1H, *J* = 16.2 Hz), 6.76 (dd, 1H, *J* = 15.6, 5.0 Hz), 7.20 (m, 5H), 7.34 (m, 5H), 7.46 (d, 1H, *J* = 7.0 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.05 (d, 1H, *J* = 5.9 Hz); MS calcd for C₃₇H₄₄N₄O₄+H 553 (M+H), found 553.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-Phe-L-(N-carbamyl-amino)-Ala]-E-Propenoate

To a stirred solution of bis (4-nitrophenyl) carbonate (66 mg, 0.22 mmol) in 2 mL CH_2Cl_2 , was added a solution of ethyl-3-[CBZ-L-Leu-L-Phe-L-amino-Ala]-E-propenoate (0.10 g, 0.18 mmol) in 2 mL CH_2Cl_2 . The mixture was stirred for 3 hours at which time 2 mL of saturated anhydrous methanolic ammonia was added. The yellow solution was allowed to stir for 30 minutes longer, diluted with 100 mL CH_2Cl_2 , and washed repeatedly with 1N NaOH to remove 4-nitrophenol. The organic layer was washed with dilute HCl, H_2O , and brine, and dried over anhydrous Na_2SO_4 . This solution was concentrated, and the residue was subjected to flash column chromatography (5% MeOH/ CH_2Cl_2) to yield a white solid in 20% yield. IR (KBr) 3470, 3291, 2978, 2926, 1715, 1645, 1539, 1281, 1045, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.81 (dd, 6H, $J = 9.0, 6.8$ Hz), 1.21 (t, 3H, $J = 7.0$ Hz), 1.30 (m, 2H), 1.48 (m, 1H), 2.92 (m, 2H), 3.10 (m, 2H), 3.97 (m, 1H), 4.10 (q, 2H, $J = 7.0$ Hz), 4.40 (m, 2H), 5.01 (m, 2H), 5.54 (bs, 2H), 5.61 (d, $J = 16.5$ Hz), 6.04 (t, 1H, $J = 7.7$ Hz), 6.71 (dd, $J = 15.8, 5.2$ Hz), 7.20 (m, 5H), 7.34 (m, 5H), 7.46 (d, 1H, $J = 7.4$ Hz), 8.01 (d, 1H, $J = 7.0$ Hz), 8.11 (d, 1H, $J = 8.5$ Hz); HRMS calcd for $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_7 + \text{Cs}$ 728.2060 (M+Cs), found 728.2078 Anal. ($\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_7$) C, H, N.

Example 10 - Preparation of Compound 17: Isopropyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate**Preparation of Intermediate 3-[BOC-L-(Tr-Gln)]-E-Propenoic Acid**

Ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (1.874 g, 3.46 mmol), prepared as described in Example 3, was taken up in 20 mL EtOH and treated with 1N NaOH solution

(7.95 mL, 7.95 mmol) dropwise, via addition funnel, over 2 hours. The resulting solution was stirred at room temperature for 1.5 hours, whereupon the reaction mixture was poured into water and washed with ether. The aqueous layer was acidified to pH 3 with 1N HCl, and extracted 3 times with EtOAc. The organic phase was separated and dried over MgSO_4 and concentrated to provide 3-[BOC-L-(Tr-Gln)]-E-propenoic acid (1.373 g, 77%) as an off-white foam. No further purification was needed: IR (thin film) 3315, 1698, 1666 cm^{-1} ; ^1H NMR(CDCl_3) δ 1.42 (s, 9H), 1.76 (m, 1H), 1.83-1.98 (m, 1H), 2.37 (t, 2H, $J = 7.0$ Hz), 4.30 (m, 1H), 4.88 (m, 1H), 5.85 (d, 1H, $J = 15.3$ Hz), 6.86 (dd, 1H, $J = 15.5, 5.1$ Hz), 6.92 (s, 1H), 7.25 (m, 15H).

Preparation of Intermediate Isopropyl-3-[BOC-L-(Tr-Gln)]-E-Propenoate

3-[BOC-L-(Tr-Gln)]-E-Propenoic acid (0.500 g, 0.973 mmol), isopropanol (0.008 mL, 1.07 mmol), and 4-dimethylaminopyridine (0.012 g, 0.0973 mmol) were taken up in 10 mL dry CH_2Cl_2 and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.196 g, 1.07 mmol). The resulting solution was stirred at room temperature overnight, concentrated in vacuo, and purified by flash column with 50% EtOAc/hexanes to provide isopropyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.106 g, 20%) as a white foam: $R_f = 0.8$ (50% EtOAc/hexanes); IR 3320, 1711 cm^{-1} ; ^1H NMR(CDCl_3) δ 1.25 (d, 6H, $J = 6.23$ Hz), 1.43 (s, 9H), 1.72 (m, 1H), 1.96 (m, 1H), 2.37 (t, 2H, $J = 7.16$ Hz), 4.30 (bs, 1H), 4.74 (m, 1H), 5.05 (m, 1H), 5.86 (dd, 1H, $J = 15.9, 5.0$ Hz), 6.78 (dd, 1H, $J = 15.6, 5.0$ Hz), 6.89 (bs, 1H), 7.26 (m, 15H); Anal. ($\text{C}_{34}\text{H}_{40}\text{N}_2\text{O}_5$) C, H, N.

Preparation of Intermediate Isopropyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate

Isopropyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.087 g, 0.191 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.079 g, 0.191 mmol) using the procedure described in Example 3 for the preparation of ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate, to provide the product (0.064 g, 40%) as a white foam: R_f = 0.7 (50% EtOAc/hexanes); IR (thin film) 3283, 1707 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.86 (m, 6H), 1.03 (m, 1H), 1.23 (m, 6H), 1.72 (m, 1H), 1.96 (m, 1H), 2.28 (m, 2H), 2.54 (m, 1H), 2.70 (m, 1H), 2.78 (m, 1H), 2.95-3.25 (m, 4H), 3.99 (m, 1H), 4.85-5.13 (m, 4H), 5.66 (d, 1H, J = 15.9 Hz), 6.45 (d, 1H, J = 7.5 Hz), 6.55 (d, 1H, J = 7.5 Hz), 6.68 (m, 1H), 7.12-7.36 (m, 25H); MS ($M+\text{Cs}$) 983.

Preparation of Product - Isopropyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate, isopropyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.059 g, 0.0694 mmol) was deprotected to provide the product (0.024 g, 57%) as a white solid: mp = 180-182 $^{\circ}\text{C}$; R_f = 0.6 (10% MeOH/ CHCl_3); IR (KBr) 3272, 1705 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.70 (m, 1H), 0.80 (dd, 6H, J = 10.6, 6.5 Hz), 1.21 (dd, 6H, J = 6.2, 2.5 Hz), 1.32 (m, 1H), 1.70 (m, 1H), 2.05 (t, 2H, J = 7.6 Hz), 2.83 (m, 1H), 2.97 (m, 1H), 3.99 (m, 1H), 4.37-4.49 (m, 4H), 4.91-5.06 (m, 4H), 5.60 (d, 1H, J = 15.3 Hz), 6.67 (dd, 1H, J = 15.6, 5.6 Hz), 6.76 (bs, 1H), 7.19 (m, 5H), 7.34 (m, 5H), 7.44 (d, 1H, J = 7.2 Hz), 8.01 (m, 2H); Anal. ($\text{C}_{27}\text{H}_{44}\text{N}_4\text{O}_7 \cdot 1.0 \text{ CH}_2\text{Cl}_2$) C, H, N.

Example 11 - Preparation of Compound 18: Cyclopentyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate**Preparation of Intermediate Cyclopentyl-3-[BOC-L-(Tr-Gln)]-E-Propenoate**

Using the procedure described in Example 10 for the preparation of isopropyl-3-[BOC-L-(Tr-Gln)]-E-propenoate, 3-[BOC-L-(Tr-Gln)]-E-propenoic acid (0.50 g, 0.973 mmol) was coupled with cyclopentanol (0.1 mL, 1.07 mmol) to provide cyclopentyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.123 g, 22%) as a white foam: $R_f = 0.7$ (EtOAc/hexanes); IR (thin film) 3319, 1708 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27 (m, 2H), 1.44 (s, 9H), 1.59-1.89 (m, 8H), 2.38 (t, 2H, $J = 7.2$ Hz), 4.32 (bs, 1H), 4.55 (m, 1H), 5.22 (m, 1H), 5.87 (d, 1H, $J = 15.6$ Hz), 6.77 (dd, 1H, $J = 15.1, 4.1$ Hz), 6.90 (bs, 1H), 7.20-7.33 (m, 15H).

Preparation of Intermediate Cyclopentyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, cyclopentyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.077 g, 0.160 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.068 g, 0.160 mmol) to provide cyclopentyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.052 g, 36%) as a white foam: $R_f = 0.4$ (50% EtOAc/hexanes); IR (thin film) 3401, 3319, 1708 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.84 (m, 6H), 1.05 (m, 1H), 1.28 (m, 1H), 1.46-1.71 (m, 9H), 1.85 (m, 1H), 2.28 (m, 2H), 2.98-3.12 (m, 4H), 3.99 (m, 1H), 4.47 (m, 2H), 4.83-5.21 (m, 4H), 5.65 (d, 1H, $J = 15.9$ Hz), 6.50 (d, 1H, $J = 7.2$ Hz), 6.59 (d, 1H, $J = 8.1$ Hz), 6.65 (dd, 1H, $J = 15.9, 5.4$ Hz), 7.04-7.35 (m, 25H); MS ($M+Cs$) 1009.

Preparation of Product - Cyclopentyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate, cyclopentyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.052 g, 0.059 mmol) was deprotected to provide the product (0.014 g, 36%) as a white solid: mp = 182-185 °C; R_f = 0.5 (10% MeOH/CHCl₃); IR (thin film) 3389, 3295, 1707 cm⁻¹; ¹H NMR (Acetone-*d*₆) δ 0.85 (dd, 6H, J = 10.6, 6.5 Hz), 1.08 (m, 1H), 1.48 (m, 1H), 1.60-1.70 (m, 11H), 1.89 (m, 1H), 2.22 (m, 2H), 2.96 (m, 1H), 3.18 (dd, 1H, J = 13.9, 5.8 Hz), 4.00 (d, 1H, J = 6.8 Hz), 4.08 (m, 1H), 4.59 (m, 2H), 4.97-5.16 (m, 4H), 5.76 (d, 1H, J = 15.3 Hz), 6.71 (m, 2H), 7.15-7.41 (m, 10H), 7.51 (d, 1H, J = 7.8 Hz); HRMS calcd for C₃₃H₄₆N₄O₇+Cs 767.2421 (M+Cs) found 767.2435.

Example 12 - Preparation of Compound 19: Cyclopentylmethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate**Preparation of Intermediate Cyclopentylmethyl-3-[BOC-L-(Tr-Gln)]-E-Propenoate**

Using the procedure described in Example 10 for the preparation of isopropyl-3-[BOC-L-(Tr-Gln)]-E-propenoate, 3-[BOC-L-(Tr-Gln)]-E-propenoic acid (0.50 g, 0.973 mmol) was coupled with cyclopentylmethanol (0.12 mL, 1.07 mmol) to provide this ester (0.298 g, 51%) as a pale yellow oil: R_f = 0.7 (50% EtOAc/hexanes); IR (thin film) 3336, 1707 cm⁻¹; ¹H NMR (CDCl₃) δ 1.28 (m, 2H), 1.43 (s, 9H), 1.54-1.62 (m, 5H), 1.72-1.78 (m, 4H), 2.37 (t, 2H, J = 7.2 Hz), 4.01 (d, 2H, J = 7.2 Hz), 4.31 (bs, 1H), 4.78 (m, 1H), 5.90 (dd, 1H, J = 15.9, 1.6 Hz), 6.80 (dd, 1H, J = 15.9, 5.3 Hz), 6.90 (bs, 1H), 7.19-7.34 (m, 15H); Anal (C₃₇H₄₄N₂O₅) C, H, N.

Preparation of Intermediate Cyclopentylmethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, cyclopentylmethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.150 g, 0.310 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.128 g, 0.310 mmol) to provide the product (0.062 g, 22%) as an off-white foam: R_f = 0.4 (50% EtOAc/hexanes); IR (thin film) 3413, 3295, 1708 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.84 (m, 6H), 1.05 (m, 1H), 1.46-1.65 (m, 10H), 1.74 (m, 1H), 2.25 (m, 2H), 2.93-3.11 (m, 4H), 3.93-4.02 (m, 3H), 4.20 (m, 1H), 4.48 (m, 1H), 4.86-5.11 (m, 4H), 5.70 (d, 1H, J = 15.0 Hz), 6.46 (d, 1H, J = 6.9 Hz), 6.54 (d, 1H, J = 8.4 Hz), 6.70 (m, 1H), 6.78 (m, 1H), 7.14-7.36 (m, 25H); MS ($\text{M}+\text{Cs}$) 1023.

Preparation of Product - Cyclopentylmethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate, cyclopentylmethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.062 g, 0.070 mmol) was deprotected to provide compound 11 (0.021 g, 47%) as a white solid: mp = 145-148 $^{\circ}\text{C}$; R_f = 0.4 (10% MeOH/ CHCl_3); IR (thin film) 3401, 3295, 1713 cm^{-1} ; ^1H NMR (acetone- d_6) δ 0.86 (dd, 6H, J = 10.6, 6.5 Hz), 1.09 (m, 1H), 1.20-1.85 (m, 13H), 2.21 (m, 2H), 2.99 (m, 1H), 3.18 (m, 1H), 3.99 (m, 2H), 4.10 (m, 2H), 4.59 (m, 2H), 4.98-5.16 (m, 4H), 5.83 (d, 1H, J = 14.6 Hz), 6.67-6.98 (m, 2H), 7.20-7.45 (m, 10H), 7.55 (m, 1H); HRMS calcd for $\text{C}_{36}\text{H}_{46}\text{N}_2\text{O}_7+\text{Cs}$ 781.2577 ($\text{M}+\text{Cs}$) found 781.2559.

Example 13 - Preparation of Compound 21: 1-Pyrrolidin-1-yl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenone**Preparation of Intermediate 1-Pyrrolidin-1-yl-3-[BOC-L-(Tr-Gln)]-E-Propenone**

3-[BOC-L-(Tr-Gln)]-E-Propenoic acid (1.09 g, 2.12 mmol) was coupled with pyrrolidine (0.18 mL, 2.12 mmol) by dissolving both in 30 mL dry CH₂Cl₂ and treating with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.610 g, 3.18 mmol), 1-hydroxybenzotriazole hydrate (0.430 g, 3.18 mmol), Et₃N (1.18 mL, 8.48 mmol) and stirring at room temperature overnight. The reaction mixture was poured into 50 mL 1N HCl, and the layers were separated. The organic layer was washed with 1N HCl and then a saturated NaHCO₃ solution. The organic layer was dried over MgSO₄ and concentrated to give a yellow residue, which was then subjected to column chromatography using a 5% MeOH/CHCl₃ to yield the product (0.661 g, 55%) as a white foam: R_f = 0.5 (5% MeOH/CHCl₃); IR (thin film) 3291, 1696 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (s, 9H), 1.89 (m, 6H), 2.37 (m, 2H), 3.44-3.53 (m, 4H), 4.28 (bs, 1H), 4.82 (d, 1H, J = 7.8 Hz), 6.17 (dd, 1H, J = 15.3, 1.6 Hz), 6.71 (dd, 1H, J = 15.4, 6.1 Hz), 6.93 (bs, 1H), 7.19-7.32 (m, 15H); Anal (C₃₃H₄₁N₃O₄·CH₂Cl₂) C, H, N.

Preparation of Intermediate 1-Pyrrolidin-1-yl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenone

Using the procedure described in Example 3 for the preparation of compound 2, ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, 1-pyrrolidin-1-yl-3-[BOC-L-(Tr-Gln)]-E-propenone (0.613 g, 1.166 mmol) was deprotected and coupled with CBZ-L-Leu-L-

Phe (0.481 g, 1.166 mmol), yielding 1-pyrrolidin-1-yl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenone (0.668 g, 67%) as a white foam: $R_f = 0.5$ (10% MeOH/CHCl₃); IR (thin film) 3294, 1702 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (m, 6H), 1.31 (m, 1H), 1.46 (m, 1H), 1.81-1.94 (m, 6H), 2.28 (m, 2H), 2.96 (m, 1H), 3.15 (m, 1H), 3.39-3.50 (m, 4H), 3.95 (m, 2H), 4.87-5.11 (m, 4H), 6.14 (d, 1H, $J = 15.3$ Hz), 6.45 (d, 1H, $J = 7.8$ Hz), 6.67 (dd, 1H, $J = 14.8$, 4.8 Hz), 6.82 (d, 1H, $J = 8.1$ Hz), 7.08-7.33 (m, 25H), 7.44 (d, 1H, $J = 8.1$ Hz); MS (M+H) 862.

Preparation of Product - 1-Pyrrolidin-1-yl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenone

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate, 1-pyrrolidin-1-yl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenone (0.668 g, 0.776 mmol) was deprotected to provide this final product (0.320 g, 67%) as a white solid: mp = 195-196 °C (dec); $R_f = 0.4$ (10% MeOH/CHCl₃); IR (thin film) 3289, 1684 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.79 (dd, 6H, $J = 12.1$, 6.5 Hz), 1.29 (m, 1H), 1.47 (m, 1H), 1.68-1.87 (m, 6H), 2.05 (m, 2H), 2.84 (m, 1H), 3.01 (m, 1H), 3.29-3.40 (m, 4H), 3.94 (m, 1H), 4.44 (m, 2H), 5.01 (m, 2H), 6.14 (d, 1H, $J = 14.9$ Hz), 6.507 (dd, 1H, $J = 15.4$, 5.8 Hz), 6.76 (bs, 1H), 7.14-7.35 (m, 10H), 7.46 (d, 1H, $J = 7.8$ Hz), 7.95-8.02 (m, 2H); HRMS calcd for C₃₄H₄₈N₆O₆, 620.3448 (M+H), found 620.3437; Anal. (C₃₄H₄₈N₆O₆·0.2 CH₂Cl₂) C, H, N.

Example 14 - Preparation of Compound 22: N,N-Dimethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenamide**Preparation of Intermediate N,N-Dimethyl-3-[BOC-L-(Tr-Gln)]-E-Propenamide**

Using the procedure described in Example 13 for the preparation of 1-pyrrolidin-1-yl-3-[BOC-L-(Tr-Gln)]-E-propenone, 3-[BOC-L-(Tr-Gln)]-E-propenoic acid (1.05 g, 2.04 mmol) was coupled with N,N-dimethylamine (0.167 g, 2.04 mmol) to provide the amide (0.848 g, 77%) as a white foam: $R_f = 0.6$ (10% MeOH/CHCl₃); IR (thin film) 3297, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (s, 9H), 1.81 (m, 1H), 1.93 (m, 1H), 2.38 (m, 2H), 2.98 (s, 3H), 3.03 (s, 3H), 4.27 (bs, 1H), 4.84 (d, 1H, $J = 7.2$ Hz), 6.31 (dd, 1H, $J = 15.1, 1.4$ Hz), 6.65 (dd, 1H, $J = 15.3, 5.9$ Hz), 6.94 (bs, 1H), 7.19-7.33 (m, 15H); Anal (C₃₁H₄₃N₃O₄·0.9 CH₂Cl₂) C, H, N.

Preparation of Intermediate N,N-Dimethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenamide

Using the procedure described in Example 3 for the preparation of compound 2, ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, N,N-dimethyl-3-[BOC-L-(Tr-Gln)]-E-propenamide (0.726 g, 1.567 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.646 g, 1.567 mmol) to provide the product (0.417 g, 32%) as a white foam: $R_f = 0.5$ (10% MeOH/CHCl₃); IR (thin film) 3291, 1702 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (m, 6H), 1.30 (m, 1H), 1.47 (m, 1H), 1.74 (m, 1H), 1.94 (m, 3H), 2.56 (s, 3H), 2.96 (m, 1H), 3.15 (m, 1H), 2.99 (d, 6H, $J = 13.4$ Hz), 3.94 (m, 1H), 4.54 (m, 2H), 4.87 (s, 2H), 5.00 (d, 2H, $J = 5.3$ Hz), 6.28 (d, 1H, $J = 14.9$ Hz), 6.42 (d, 1H, $J = 7.8$ Hz), 6.63 (dd, 1H, $J = 15.3, 5.0$ Hz),

6.81 (d, 1H, $J = 8.4$ Hz), 7.06 (bs 1H), 7.10-7.36 (m, 25H); Anal ($C_{51}H_{59}N_5O_8 \cdot 3.0 H_2O$) C, H, N.

Preparation of Product - N,N-Dimethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenamide

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenoate, N,N-dimethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenamide (0.417 g, 0.5 mmol) was deprotected to provide N,N-dimethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-propenamide (0.214 g, 72%) as a white solid: mp = 174-175 °C (dec); $R_f = 0.34$ (MeOH/ $CHCl_3$); IR (thin film) 3284, 1684 cm^{-1} ; 1H NMR (DMSO- d_6) δ 0.79 (dd, 6H, $J = 12.1, 6.5$ Hz), 1.30 (m, 1H), 1.47 (m, 1H), 1.70 (m, 2H), 2.06 (m, 2H), 2.84 (m, 1H), 2.98 (s, 3H), 3.03 (s, 3H), 3.94 (m, 1H), 4.44 (m, 2H), 4.95-5.07 (m, 4H), 6.27 (d, 1H, $J = 15.3$ Hz), 6.47 (dd, 1H, $J = 15.3, 5.6$ Hz), 6.75 (bs, 1H), 7.14-7.35 (m, 10H), 7.46 (d, 1H, $J = 7.5$ Hz), 7.96-8.01 (m, 2H); HRMS calcd for $C_{37}H_{45}N_5O_6$ 594.3291 (M+H), found 594.3281. Anal. ($C_{37}H_{45}N_5O_6 \cdot 1.0 CH_2Cl_2$) C, H, N.

Example 15 - Preparation of Compound 24: 1-Phenyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenone

Preparation of Intermediate 2-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Vinyl) Pyridine

2-Picolyltriphenylphosphonium chloride/ $NaNH_4$ (0.345 g, 0.76 mmol) was dissolved in 10 mL of THF. CBZ-L-Leu-L-Phe-L-(Tr-Glutaminal) (0.53 g, 0.69 mmol) was dissolved in 5 mL of THF and added dropwise to the yield solution at room temperature, which was allowed to stir overnight. The solvent was removed in vacuo, and the crude

product purified by column chromatography eluting with a gradient of 1-5% MeOH in CHCl₃ to give 0.353 g (61%) of a white glassy solid: IR (KBr) 3295, 3061, 2953, 1952, 1881, 1649, 1539, 1234, 1045, 972, 750, 696 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.78 (t, 6H, *J* = 7.0 Hz), 1.30 (m, 2H), 1.46 (m, 1H), 1.70 (m, 2H), 2.27 (m, 2H), 2.78 (m, 1H), 3.03 (m, 1H), 3.97 (m, 1H), 4.42 (m, 1H), 4.52 (m, 1H), 4.96 (d, 1H, *J* = 12.0 Hz), 5.03 (d, 1H, *J* = 12.0 Hz), 6.38 (d, 1H, *J* = 16.0 Hz), 6.60 (dd, 1H, *J* = 16.0, 6.0 Hz), 7.10-7.34 (m, 27H), 7.42 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 8.5 Hz), 8.07 (d, 1H, *J* = 8.5 Hz), 8.49 (d, 1H, *J* = 5.0 Hz), 8.59 (s, 1H); MS (M+H) 842. Anal. (C₃₃H₃₃N₃O₃·0.75 H₂O) C, H, N.

Preparation of Intermediate 2-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Pyridine

Using the procedure described in Example 32 for the preparation of compound 20, diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-vinyl] phosphonate, 2-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-vinyl] pyridine was synthesized from 2-(CBZ-L-Leu-L-Phe-L-Tr-Gln)-E-vinyl pyridine in 69% yield as a white solid: IR (KBr) 3291, 3059, 2955, 2359, 1694, 1641, 1539, 1234, 1119, 1047, 970, 743, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.78 (m, 6H), 1.32 (m, 2H), 1.49 (m, 1H), 1.77 (m, 2H), 2.11 (t, 2H, *J* = 7.0 Hz), 2.86 (m, 1H), 3.01 (m, 1H), 3.96 (m, 1H), 4.41 (m, 1H), 4.51 (m, 1H), 4.98 (d, 1H, *J* = 13.0 Hz), 5.04 (d, 1H, *J* = 13.0 Hz), 6.39 (d, 1H, *J* = 16.0 Hz), 6.60 (dd, 1H, *J* = 16.0, 6.0 Hz), 6.75 (bs, 1H), 7.08-7.34 (m, 13H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.73 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 8.50 (d, 1H, *J* = 4.0 Hz); HRMS calcd for C₃₄H₄₄N₃O₃, 600.3186 (M+H), found 600.3198. Anal. (C₃₄H₄₄N₃O₃·1.0 H₂O) C, H, N.

Preparation of Intermediate 1-Phenyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenone

Using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate, this compound was synthesized from CBZ-L-Leu-L-Phe-L-Tr-glutamine and (benzoylmethylene)triphenylphosphorane to give 0.38 g of crude material (impure with triphenylphosphine oxide), which was used without further purification.

Preparation of Product - 1-Phenyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenone

To 0.38 g of 1-phenyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenone, impure with triphenylphosphine oxide, was added 10 mL of CH_2Cl_2 . TFA (1 mL) was added to this solution, and the reaction was stirred at room temperature for four hours. The reaction was poured into an EtOAc/saturated NaHCO_3 solution and agitated until white solids began to precipitate out of the organic layer. The aqueous layer was separated, and the solids filtered and washed with EtOAc to give compound 14 (0.0795 g, 20% yield from the aldehyde; 2 steps) as a white solid: IR (KBr) 3408, 3293, 3063, 2955, 1653, 1539, 1449, 1283, 1234, 1121, 1047, 970, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.78 (m, 6H), 1.31 (m, 2H), 1.45 (m, 1H), 1.76 (m, 2H), 2.11 (t, 2H, $J = 8.0$ Hz), 2.89 (m, 1H), 3.01 (m, 1H), 3.97 (m, 1H), 4.51 (m, 2H), 4.97 (d, 1H, $J = 13.0$ Hz), 5.05 (d, 1H, $J = 13.0$ Hz), 6.76 (dd, 1H, $J = 15.0, 5.0$ Hz), 6.77 (bs, 1H), 6.91 (d, 1H, $J = 15.0$ Hz), 7.02-7.34 (m, 11H), 7.47 (d, 1H, $J = 7.0$ Hz), 7.54 (m, 2H), 7.66 (t, 1H, $J = 7.0$ Hz), 7.93 (d, 2H, $J = 7.0$ Hz), 8.04 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 1H, $J = 8.5$ Hz); HRMS calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_4$, 627.3182 (M+H), found 627.3199. Anal. ($\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_4$) C, H, N.

Example 16 - Preparation of Compound 26: Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-Gln]-E-Propenoate

Preparation of Intermediate BOC-L-(4-Cl-Phe)-L-(Tr-Glutaminol)

BOC-L-4-Cl-Phe (0.90 g, 3.0 mmol) was dissolved in 30 mL of THF.

Carbonyldiimidazole (0.49 g, 3.0 mmol) was added, and the reaction was allowed to stir at room temperature for one hour. L-(Tr-Glutaminol) (1.12 g, 3 mmol) was added, and the reaction was stirred overnight at room temperature. The solvent was removed in vacuo, and the product was purified by flash column chromatography eluting with 3% MeOH/CHCl₃ to yield 1.57 g (80%) of a white solid: IR (KBr) 3416, 3302, 3057, 3024, 2978, 2934, 1663, 1491, 1447, 1366, 1250, 1165, 752, 700 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.28 (s, 9H), 1.44 (m, 1H), 1.66 (m, 1H), 2.26 (m, 2H), 2.72 (m, 1H), 2.91 (m, 1H), 3.18 (m, 2H), 3.64 (m, 1H), 4.07 (m, 1H), 4.67 (t, 1H, *J* = 5.0 Hz), 7.05-7.32 (m, 19H), 6.86 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 8.5 Hz), 8.48 (s, 1H). Anal. (C₃₁H₄₁N₃O₅Cl·1.0 H₂O) C, H, N.

Preparation of Intermediate L-(4-Cl-Phe)-L-(Tr-Glutaminol) Hydrochloride Salt

BOC-L-(4-Cl-Phe)-L-(Tr-Glutaminol) (1.57 g, 2.4 mmol) was dissolved in a minimum amount of CH₂Cl₂ (~ 5 mL) followed by 50 mL of Et₂O. Anhydrous HCl gas was bubbled into the solution until a white solid precipitated from solution. The reaction was allowed to stir at room temperature overnight, and the resulting solid was filtered and washed with Et₂O, giving 1.19 g (84%) of a white crystalline material: IR (KBr) 3246,

3057, 3028, 2934, 1668, 1494, 1447, 1089, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.48 (m, 1H), 1.71 (m, 1H), 2.30 (m, 2H), 2.94-3.17 (m, 3H), 3.27 (m, 1H), 3.67 (br, 2H), 3.98 (m, 1H), 7.07-7.40 (m, 19H), 8.28 (bs, 3H), 8.34 (d, 1H, $J = 8.8$ Hz), 8.54 (s, 1H). Anal. ($\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_5\text{Cl}\cdot 1.0\text{HCl}\cdot 0.75\text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-(Tr-Glutaminol)

4-Methoxyindole-2-carboxylic acid (0.36 g, 1.87 mmol) was suspended in 10 mL of CH_2Cl_2 . To this suspension was added N-hydroxysuccinimide (0.23 g, 1.97 mmol) and 2 mL of DMF to dissolve all solids. Dicyclohexylcarbodiimide (0.41 g, 1.97 mmol) was added, and the reaction mixture was stirred at room temperature for 4 hours. At this time the mixture was then filtered into a separate flask containing (1.17 g, 1.97 mmol) of L-(4-Cl-Phe)-L-(Tr-glutaminol)HCl salt, 0.41 mL (2.95 mmol) of Et_3N , 10 mL of CH_2Cl_2 , and 2 mL of DMF, removing the N,N'-dicyclohexylurea precipitate. The reaction was allowed to stir overnight at room temperature. The solvents were removed in vacuo, and the resulting crude product was purified by flash column chromatography eluting with 3% (anhydrous NH_3/MeOH)/ CHCl_3 to afford 0.53 g (39%) of a white solid: IR (KBr) 3290, 3057, 2933, 1653, 1491, 1360, 1257, 1098, 754, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.50 (m, 1H), 1.74 (m, 1H), 2.28 (m, 2H), 3.02 (m, 2H), 3.24 (m, 2H), 3.66 (m, 1H), 3.87 (s, 3H), 4.65 (m, 1H), 4.70 (m, 1H), 6.49 (m, 1H, $J = 7.3$ Hz), 6.94-7.38 (m, 22H), 7.86 (d, 1H, $J = 8.8$ Hz), 8.49 (d, 1H, $J = 8.8$ Hz), 8.53 (s, 1H), 11.50 (s, 1H). Anal. ($\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_5\text{Cl}\cdot 0.75\text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-(Tr-Glutaminal)

N-(4-Methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminol) (1.13 g, 1.55 mmol) was dissolved in 15 mL of DMSO. o-Iodoxybenzoic acid (1.30 g, 4.66 mmol) was added to this solution, and dissolved after a few minutes of stirring at room temperature. After two hours the DMSO was removed under reduced pressure. The residue was twice diluted with CH₂Cl₂, and the solvent was evaporated to remove any residual DMSO. The residue was diluted with EtOAc, and the white precipitate was triturated and filtered off. The organic solvent was washed with 10% Na₂S₂O₃/10% NaHCO₃ solution, water, and brine before drying over Na₂SO₄. The solvent was removed to give 0.85 g (76%) of a white glassy solid which was used immediately without further purification: ¹H NMR (DMSO-*d*₆) δ 1.72 (m, 2H), 2.32 (m, 2H), 3.04 (m, 1H), 3.11 (m, 1H), 3.87 (m, 3H), 4.05 (m, 1H), 4.81 (m, 1H), 6.49 (d, 1H, *J* = 7.3 Hz), 6.94-7.39 (m, 22H), 8.60 (m, 2H), 8.63 (s, 1H), 9.34 (s, 1H), 11.48 (s, 1H).

Preparation of Intermediate Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate, this compound was synthesized from N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminal) in 59% yield as a white solid: IR (KBr) 3302, 3057, 2934, 1958, 1896, 1659, 1491, 1260, 1096, 1036, 833, 756, 700 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.22 (t, 3H, *J* = 6.0 Hz), 1.72 (m, 2H), 2.24 (m, 2H), 3.05 (m, 2H), 3.88 (s, 3H), 4.12 (q, 2H, *J* = 6.0 Hz), 4.43 (m, 1H), 4.78 (m, 1H), 5.74 (d,

1H, $J = 14.0$ Hz), 6.50 (d, 1H, $J = 7.7$ Hz), 6.77 (dd, 1H, $J = 16.0, 5.0$ Hz), 6.93-7.57 (m, 22H), 8.33 (d, 1H, $J = 7.7$ Hz), 8.56 (d, 1H, $J = 7.7$ Hz), 8.60 (s, 1H), 11.51 (s, 1H). Anal. ($C_{44}H_{48}N_4O_4Cl \cdot 0.5 H_2O$) C, H, N.

Preparation of Product - Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-Gln]-E-Propenoate

Using the procedure described in Example 32 for the preparation of compound 20, diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-vinyl] phosphonate, this compound was synthesized by deprotection of ethyl-3-[N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-Gln)]-E-propenoate. The product was purified by flash silica gel chromatography eluting with 2-3% MeOH/CHCl₃ to give 0.16 g (73%) of an off-yellow solid: IR (KBr) 3420, 3289, 2930, 2838, 1722, 1663, 1622, 1541, 1261, 1184, 1101, 976, 754 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.21 (t, 3H, $J = 7.0$ Hz), 1.74 (m, 2H), 2.11 (t, 2H, $J = 8.0$ Hz), 3.02 (m, 2H), 3.88 (s, 3H), 4.12 (q, 2H, $J = 7.0$ Hz), 4.42 (m, 1H), 4.68 (m, 1H), 5.74 (dd, 1H, $J = 16.0, 1.5$ Hz), 6.47 (d, 1H, $J = 5.0$ Hz), 6.75 (bs, 1H), 6.76-6.81 (m, 2H), 6.96 (d, 1H, $J = 8.5$ Hz), 7.07 (t, 1H, $J = 8.0$ Hz), 7.24-7.38 (m, 5H), 8.33 (d, 1H, $J = 8.0$ Hz), 8.58 (d, 1H, $J = 8.5$ Hz), 11.52 (s, 1H); HRMS calcd for $C_{44}H_{48}N_4O_4Cl + Cs$ 687.0986 (M+Cs), found 687.0976. Anal. ($C_{44}H_{48}N_4O_4Cl$) C, H, N.

Example 17 - Preparation of Compound 27: Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(4-F-Phe)-L-Gln]-E-Propenoate

Preparation of Intermediate BOC-L-(4-F-Phe)-L-(Tr-Glutaminol)

Using the procedure described in Example 16 for the preparation of BOC-L-(4-Cl-Phe)-L-(Tr-glutaminol), this compound was synthesized from BOC-L-4-F-Phe and L-(Tr-glutaminol) in 80% yield. White solid: IR (KBr) 3416, 3308, 3057, 2978, 2932, 1663, 1510, 1368, 1223, 1167, 1051, 752, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.28 (s, 9H), 1.44 (m, 1H), 1.68 (m, 1H), 2.25 (m, 2H), 2.70 (m, 1H), 2.90 (m, 1H), 3.25 (m, 2H), 3.63 (m, 1H), 4.10 (m, 1H), 4.67 (t, 1H, $J = 5.0$ Hz), 7.04-7.28 (m, 19H), 6.85 (d, 1H, $J = 8.5$ Hz), 7.61 (d, 1H, $J = 8.0$ Hz), 8.48 (s, 1H). Anal. ($\text{C}_{31}\text{H}_{42}\text{N}_4\text{O}_5 \cdot 0.75 \text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate L-(4-F-Phe)-L-(Tr-Glutaminol) Hydrochloride Salt

Using the procedure described in Example 16 for the preparation of L-(4-Cl-Phe)-L-(Tr-glutaminol)hydrochloride salt, this salt was synthesized from BOC-L-(4-F-Phe)-L-(Tr-glutaminol) in 79% yield. White crystalline solid: IR (KBr) 3245, 3057, 2361, 1668, 1510, 1447, 1223, 766, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.47 (m, 1H), 1.72 (m, 1H), 2.30 (m, 2H), 2.94-3.16 (m, 3H), 3.23 (m, 1H), 3.65 (bs, 2H), 3.95 (m, 1H), 7.09-7.32 (m, 19H), 8.28 (m, 4H), 8.54 (s, 1H). Anal. ($\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_5 \cdot 1.0 \text{HCl} \cdot 1.0 \text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(4-F-Phe)-L-(Tr-Glutaminol)

Using the procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminol), this intermediate was synthesized from 4-methoxyindole-2-carboxylic acid and L-(4-F-Phe)-L-(Tr-

glutaminol)HCl salt, in 40% yield. White solid: IR (KBr) 3314, 3059, 2938, 1956, 1888, 1653, 1510, 1361, 1255, 1097, 835, 756, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.58 (m, 1H), 1.81 (m, 1H), 2.28 (m, 2H), 3.02 (m, 2H), 3.23 (m, 2H), 3.67 (m, 1H), 3.87 (s, 3H), 4.69 (m, 2H), 6.49 (m, 1H, $J = 7.3$ Hz), 6.94-7.39 (m, 22H), 7.84 (d, 1H, $J = 8.5$ Hz), 8.48 (d, 1H, $J = 8.5$ Hz), 8.53 (s, 1H), 11.49 (s, 1H). Anal. ($\text{C}_{40}\text{H}_{41}\text{N}_4\text{O}_3\text{F}\cdot 1.0\text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(4-F-Phe)-L-(Tr-Glutaminal)

Using the oxidation procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminal), this aldehyde was prepared in 80% yield from N-(4-methoxyindole-2-carbonyl)-L-(4-F-Phe)-L-(Tr-glutaminol). Glassy white solid: ^1H NMR ($\text{DMSO}-d_6$) δ 1.72 (m, 2H), 2.37 (m, 2H), 3.03 (m, 1H), 3.17 (m, 1H), 3.87 (s, 3H), 4.09 (m, 1H), 4.74 (m, 1H), 6.49 (d, 1H, $J = 7.7$ Hz), 6.94-7.41 (m, 22H), 8.58 (m, 2H), 8.63 (s, 1H), 9.32 (s, 1H), 11.49 (s, 1H).

Preparation of Intermediate Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(4-F-Phe)-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate, this vinyl ester was synthesized from N-(4-methoxyindole-2-carbonyl)-L-(4-F-Phe)-L-(Tr-glutaminal) and (carbethoxymethylenc)triphenyl-phosphorane in 60% yield. White solid: IR (KBr) 3300, 3061, 2938, 1958, 1890, 1653, 1510, 1368, 1260, 1100, 1036, 835, 756, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.20 (t, 3H, $J = 7.0$ Hz), 1.70 (m, 2H), 2.35 (m, 2H), 3.01 (m, 2H), 3.87 (s,

3H), 4.11 (q, 2H, $J = 7.0$ Hz), 4.41 (m, 1H), 4.67 (m, 1H), 5.68 (d, 1H, $J = 16.0$ Hz), 6.49 (d, 1H, $J = 7.7$ Hz), 6.74 (dd, 1H, $J = 16.0, 5.0$ Hz), 6.97-7.38 (m, 22H), 8.31 (d, 1H, $J = 8.5$ Hz), 8.55 (d, 1H, $J = 8.5$ Hz), 8.58 (s, 1H), 11.51 (s, 1H). Anal. ($C_{47}H_{41}N_4O_6F \cdot 1.0H_2O$) C, H, N.

Preparation of Product - Ethyl-3-[N-(4-Methoxyindolc-2-Carbonyl)-L-(4-F-Phe)-L-Gln]-E-Propenoate

Using the procedure described in Example 32 for the preparation of compound 20, diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-vinyl] phosphonate, this compound was synthesized by deprotection of ethyl-3-[N-(4-methoxyindole-2-carbonyl)-L-(4-F-Phe)-L-(Tr-Gln)]-E-propenoate in 50% yield: White crystalline solid: IR (KBr) 3422, 3293, 2932, 1719, 1665, 1620, 1541, 1510, 1369, 1261, 1182, 1101, 752 cm^{-1} ; 1H NMR (DMSO- d_6) δ 1.21 (t, 3H, $J = 7.0$ Hz), 1.73 (m, 2H), 2.10 (t, 2H, $J = 8.0$ Hz), 3.02 (m, 2H), 3.88 (s, 3H), 4.13 (q, 2H, $J = 7.0$ Hz), 4.43 (m, 1H), 4.67 (m, 1H), 5.67 (dd, 1H, $J = 16.0, 1.5$ Hz), 6.49 (d, 1H, $J = 7.0$ Hz), 6.75 (bs, 1H), 6.76 (dd, 1H, $J = 16.0, 5.5$ Hz), 6.96 (d, 1H, $J = 8.5$ Hz), 7.03-7.10 (m, 3H), 7.23 (bs, 1H), 7.31-7.39 (m, 3H), 8.31 (d, 1H, $J = 8.0$ Hz), 8.57 (d, 1H, $J = 8.0$ Hz), 11.51 (s, 1H); HRMS calcd for $C_{47}H_{41}N_4O_6F + Cs$ 671.1282 (M+Cs), found 671.1288. Anal. ($C_{47}H_{41}N_4O_6F$) C, H, N.

Example 18 - Preparation of Compound 28: Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(3-F-Phe)-L-Gln]-E-Propenoate

Preparation of Intermediate BOC-L-(3-F-Phe)-L-(Tr-Glutaminol)

Using the procedure described in Example 16 for the preparation of BOC-L-(4-Cl-Phe)-L-(Tr-glutaminol), this compound was synthesized from BOC-L-3-F-Phe and L-(Tr-glutaminol) in 74% yield. White solid: IR (KBr) 3410, 3302, 3059, 3030, 2974, 2934, 1663, 1491, 1448, 1250, 1167, 1051, 752, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.28 (s, 9H), 1.46 (m, 1H), 1.71 (m, 1H), 2.26 (m, 2H), 2.74 (m, 1H), 2.95 (m, 1H), 3.19 (m, 2H), 3.65 (m, 1H), 4.11 (m, 1H), 4.67 (t, 1H, $J = 5.0$ Hz), 6.97-7.32 (m, 19H), 6.89 (d, 1H, $J = 8.5$ Hz), 7.58 (d, 1H, $J = 8.5$ Hz), 8.48 (s, 1H). Anal. ($\text{C}_{31}\text{H}_{40}\text{N}_3\text{O}_5\text{F} \cdot 1.0 \text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate L-(3-F-Phe)-L-(Tr-Glutaminol) Hydrochloride Salt

Using the procedure described in Example 16 for the preparation of L-(4-Cl-Phe)-L-(Tr-glutaminol) hydrochloride salt, this salt was synthesized from BOC-L-(3-F-Phe)-L-(Tr-glutaminol) in 88% yield. White crystalline solid: IR (KBr) 3231, 3047, 1668, 1491, 1447, 1254, 1145, 1036, 752, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.45 (m, 1H), 1.72 (m, 1H), 2.30 (m, 2H), 2.96-3.11 (m, 3H), 3.25 (m, 1H), 3.70 (m, 1H), 4.03 (m, 1H), 7.06-7.38 (m, 19H), 8.30 (bs, 4H), 8.54 (s, 1H). Anal. ($\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_5\text{F} \cdot 1.0 \text{HCl} \cdot 0.5 \text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(3-F-Phe)-L-(Tr-Glutaminol)

Using the procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminol), this intermediate was synthesized from 4-methoxyindole-2-carboxylic acid and L-(3-F-Phe)-L-(Tr-glutaminol)HCl salt, in 60% yield. White solid: IR (KBr) 3291, 3057, 2936, 1956, 1890, 1653, 1361, 1256, 1100, 754, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.58 (m, 1H), 1.81 (m, 1H), 2.28 (m, 2H), 3.02 (m, 2H), 3.28 (m, 2H), 3.70 (m, 1H), 3.87 (s, 3H), 4.68 (m, 2H), 6.49 (m, 1H, $J = 7.7$ Hz), 6.94-7.28 (m, 22H), 7.85 (d, 1H, $J = 8.5$ Hz), 8.50 (d, 1H, $J = 8.5$ Hz), 8.53 (s, 1H), 11.50 (s, 1H). Anal. ($\text{C}_{33}\text{H}_{41}\text{N}_5\text{O}_5 \cdot 1.0\text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate N-(4-Methoxyindole-2-Carbonyl)-L-(3-F-Phe)-L-(Tr-Glutaminal)

Using the oxidation procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminal), this aldehyde was prepared in 77% yield from N-(4-methoxyindole-2-carbonyl)-L-(3-F-Phe)-L-(Tr-glutaminol) and was used immediately. Glassy white solid: ^1H NMR ($\text{DMSO}-d_6$) δ 1.68 (m, 2H), 2.37 (m, 2H), 3.04 (m, 1H), 3.18 (m, 1H), 3.87 (m, 3H), 4.05 (m, 1H), 4.81 (m, 1H), 6.49 (d, 1H, $J = 7.7$ Hz), 6.94-7.30 (m, 22H), 8.60 (m, 2H), 8.62 (s, 1H), 9.33 (s, 1H), 11.48 (s, 1H).

Preparation of Intermediate Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(3-F-Phe)-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-*Met*(sulfoxide)-E-propenoate, this vinyl ester was synthesized from N-(4-methoxyindole-2-carbonyl)-L-(3-F-Phe)-L-(Tr-glutaminal) and (carbethoxymethylene)triphenyl-phosphorane in 68% yield. White solid: IR (KBr) 3293, 3057, 2934, 1956, 1894, 1657, 1491, 1368, 1260, 1100, 1036, 978, 756, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.20 (t, 3H, $J = 7.0$ Hz), 1.69 (m, 2H), 2.25 (m, 2H), 3.02 (m, 2H), 3.87 (s, 3H), 4.11 (q, 2H, $J = 7.0$ Hz), 4.42 (m, 1H), 4.69 (m, 1H), 5.71 (d, 1H, $J = 16.0$ Hz), 6.49 (d, 1H, $J = 8.0$ Hz), 6.75 (dd, 1H, $J = 16.0, 5.0$ Hz), 6.91-7.29 (m, 22H), 8.32 (d, 1H, $J = 8.0$ Hz), 8.56 (d, 1H, $J = 8.0$ Hz), 8.59 (s, 1H), 11.51 (s, 1H). Anal. ($\text{C}_{44}\text{H}_{46}\text{N}_4\text{O}_6\text{F}0.5\text{H}_2\text{O}$) C, H, N.

Preparation of Product - Ethyl-3-[N-(4-Methoxyindole-2-Carbonyl)-L-(3-F-Phe)-L-Gln]-E-Propenoate

Using the procedure described in Example 32 for the preparation of compound 20, diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-vinyl]phosphonate, this compound was synthesized by deprotection of ethyl-3-[N-(4-methoxyindole-2-carbonyl)-L-(3-F-Phe)-L-(Tr-Gln)]-E-propenoate in 52% yield. White solid: IR (KBr) 3283, 2932, 1663, 1539, 1370, 1256, 1188, 1098, 1036, 978, 752 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.21 (t, 3H, $J = 7.0$ Hz), 1.73 (m, 2H), 2.11 (t, 2H, $J = 7.0$ Hz), 3.07 (m, 2H), 3.88 (s, 3H), 4.11 (q, 2H, $J = 7.0$ Hz), 4.49 (m, 1H), 4.75 (m, 1H), 5.72 (dd, 1H, $J = 16.0, 1.5$ Hz), 6.49 (d, 1H, $J = 7.7$ Hz), 6.80 (m, 2H),

6.98-7.31 (m, 8H), 8.32 (d, 1H, $J = 8.0$ Hz), 8.58 (d, 1H, $J = 8.0$ Hz), 11.52 (s, 1H); HRMS calcd for $C_{21}H_{21}N_4O_6F$ 539.2306 (M+H), found 539.2317. Anal. ($C_{21}H_{21}N_4O_6F$) C, H, N.

Example 19 - Preparation of Compound 30: Ethyl-3-(CBZ-L-Phe-L-Gln)-E-Propenoate

Preparation of Intermediate Ethyl-3-[CBZ-L-Phe-L-(Tr-Gln)]-E-Propenoate

Ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.60 g, 1.1 mmol), prepared as in Example 3, was deprotected and coupled with CBZ-L-Phe (0.31 g, 1.04 mmol) using the procedure described in Example 28 for the preparation of ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate to provide ethyl-3-[CBZ-L-Phe-L-(Tr-Gln)]-E-propenoate (0.400 g, 53%) as a white foam: IR (thin film) 3298, 1651 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.21 (t, 3H, $J = 7.2$ Hz), 1.65-1.75 (m, 1H), 1.90-1.93 (m, 1H), 2.29 (s, br, 2H), 2.98-3.00 (m, 2H), 4.12 (q, 2H, $J = 7.2$ Hz), 4.25-4.30 (m, 1H), 4.93 (d, 1H, $J = 12.3$ Hz), 4.50 (s, br, 1H), 5.01 (d, 1H, $J = 12.3$ Hz), 5.23 (d, 1H, $J = 6.2$ Hz), 5.63 (d, 1H, $J = 15.6$ Hz), 6.39 (d, 1H, $J = 7.2$ Hz), 6.61 (dd, 1H, $J = 15.6, 5.6$ Hz), 6.79 (s, 1H), 7.11-7.34 (m, 25H); Anal. ($C_{24}H_{24}N_3O_6$) C, H, N.

Preparation of Product - Ethyl-3-(CBZ-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, Ethyl-3-[CBZ-L-Phe-L-(Tr-Gln)]-E-propenoate (0.40 g, 0.58 mmol) was deprotected to provide ethyl-3-(CBZ-L-Phe-L-Gln)-E-propenoate (0.15 g, 78%) as a white solid: mp = 184-186 $^{\circ}C$; IR (thin film) 3287, 1637, 1533 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 1.21 (t, 3H, $J =$

7.2 Hz), 1.64-1.80 (m, 2H), 2.08 (t, 2H, $J = 7.6$ Hz), 2.73-2.80 (m, 1H), 2.94 (dd, 1H, $J = 13.7, 5.3$ Hz), 4.11 (q, 2H, $J = 7.2$ Hz), 4.20-4.26 (m, 1H), 4.28-4.39 (m, 1H), 4.95 (s, 2H), 5.69 (d, 1H, $J = 15.9$ Hz), 6.70 (d, 1H, $J = 5.3$ Hz), 6.75-6.77 (m, 2H), 7.17-7.35 (m, 1H), 7.53 (d, 1H, $J = 8.4$ Hz), 8.20 (d, 1H, $J = 8.1$ Hz); Anal. ($C_{26}H_{31}N_3O_6$) C, H, N.

Example 20 - Preparation of Compound 31: Ethyl-3-[N-(Propylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

Preparation of Intermediate Ethyl-3-[BOC-L-Phe-L-(Tr-Gln)]-E-Propenoate

Ethyl-3-[BOC-L-(Tr-Gln)]-E-propenoate (2.26 g, 4.16 mmol), prepared as in Example 3, was dissolved in 1,4-dioxane (15 mL). A solution of HCl in 1,4-dioxane (4.0 M, 15 mL) was added dropwise. The reaction solution was stirred at room temperature for 2 hours, then poured into a solution of aqueous NaOH (1 M, 80 mL) in saturated aqueous $NaHCO_3$ (120 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the free amine intermediate as a slightly yellow solid, which was used without further purification. This crude amine, BOC-L-Phe (1.10 g, 4.15 mmol), and 1-hydroxybenzotriazole hydrate (0.843 g, 6.24 mmol) were stirred in dry CH_2Cl_2 (35 mL) under argon at room temperature. 4-Methylmorpholine (1.83 mL, 16.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.20 g, 6.26 mmol) were added sequentially. After stirring for 3.5 hours, the reaction mixture was poured into water (100 mL), and the mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (33% acetone in hexanes) to give the product (1.94 g, 68%) as a white foam: IR (thin film) 3413,

3310, 1708, 1660 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.30 (t, 3H, $J = 7.2$ Hz), 1.39 (s, 9H), 1.64-1.77 (m, 1H), 1.88-2.00 (m, 1H), 2.25-2.31 (m, 2H), 2.94-3.07 (m, 2H), 4.18 (q, 2H, $J = 7.2$ Hz), 4.49-4.59 (m, 1H), 4.95 (bs, 1H), 5.66 (d, 1H, $J = 15.9$ Hz), 6.29 (m, 1H), 6.64 (dd, 1H, $J = 15.9, 5.3$ Hz), 6.81 (bs, 1H), 7.14-7.34 (m, 21H); Anal. ($\text{C}_{42}\text{H}_{47}\text{N}_3\text{O}_6$) C, H, N.

Preparation of Intermediate Ethyl-3-[L-Phe-L-(Tr-Gln)]-E-Propenoate

Ethyl-3-[BOC-L-Phe-L-(Tr-Gln)]-E-propenoate (0.300 g, 0.435 mmol) was dissolved in 1,4-dioxane (2 mL). A solution of HCl in 1,4-dioxane (4.0 M, 2 mL) was added dropwise. The reaction solution was stirred at room temperature for 2.5 hours, then poured into a solution of aqueous NaOH (1 M, 10 mL) in saturated aqueous NaHCO_3 (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the product as a foam (0.257 g, quantitative) which was used without further purification.

Preparation of Intermediate Ethyl-3-[N-(Propylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-Propenoate

Ethyl-3-[L-Phe-L-(Tr-Gln)]-E-propenoate was dissolved in dry CH_2Cl_2 (7 mL) under argon and cooled to 0 °C. NEt₃ (0.067 mL, 0.48 mmol) and 1-propanesulfonyl chloride (0.054 mL, 0.48 mmol) were added sequentially. After stirring for 1 hour, the reaction mixture was allowed to warm to room temperature. More NEt₃ (0.100 mL, 0.714 mmol) and 1-propanesulfonyl chloride (0.086 mL, 0.76 mmol) were added. After 1.5 hours more, the solvent was evaporated and the residue was purified by column chromatography (50%

EtOAc in hexanes) to give the product as a foam (0.121 g, 40%): IR (thin film) 3292, 1713, 1652, 1312, 1144 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.80 (t, 3H, $J = 7.5$ Hz), 1.28 (t, 3H, $J = 7.2$ Hz), 1.34-1.58 (m, 2H), 1.67-1.81 (m, 1H), 1.92-2.04 (m, 1H), 2.32-2.56 (m, 4H), 2.79 (dd, 1H, $J = 13.9, 8.9$ Hz), 3.05 (dd, 1H, $J = 13.9, 5.5$ Hz), 3.96-4.05 (m, 1H), 4.17 (q, 2H, $J = 7.2$ Hz), 4.49-4.59 (m, 1H), 5.14 (d, 1H, $J = 8.7$ Hz), 5.75 (dd, 1H, $J = 15.9, 1.7$ Hz), 6.72 (dd, 1H, $J = 15.9, 5.3$ Hz), 6.94 (s, 1H), 7.02 (d, 1H, $J = 8.1$ Hz), 7.12-7.33 (m, 20H); HRMS ($\text{M} + \text{Cs}$) calcd for $\text{C}_{40}\text{H}_{45}\text{N}_3\text{O}_6\text{S}$ 828.2083, found 828.2063.

Preparation of Product - Ethyl-3-[N-(Propylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

Ethyl-3-[N-(propylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate (0.100 g, 0.143 mmol) was dissolved in $\text{CH}_2\text{Cl}_2/\text{TFA}$ 1:1 (4 mL) under argon. The bright yellow solution was stirred at room temperature for 30 minutes. CCl_4 (4 mL) was added and the solution was concentrated to dryness. The residue was triturated with Et_2O (3 mL) to give a white precipitate which was collected by filtration and washed with Et_2O (2 x 2 mL) to give the product (0.048 g, 74%): mp = 161-162 $^\circ\text{C}$; IR (KBr) 3284, 3213, 1708, 1666, 1543, 1314, 1138 cm^{-1} ; ^1H NMR (acetone- d_6) δ 0.83 (t, 3H, $J = 7.5$ Hz), 1.25 (t, 3H, $J = 7.2$ Hz), 1.39-1.62 (m, 2H), 1.73-2.02 (m, 2H), 2.23-2.30 (m, 2H), 2.54-2.72 (m, 2H), 2.92 (dd, 1H, $J = 13.5, 8.9$ Hz), 3.15 (dd, 1H, $J = 13.5, 6.1$ Hz), 4.14 (q, 2H, $J = 7.2$ Hz), 4.12-4.21 (m, 1H), 4.53-4.63 (m, 1H), 5.79 (dd, 1H, $J = 15.7, 1.7$ Hz), 6.18 (bs, 1H), 6.30 (d, 1H, $J = 8.7$ Hz), 6.78 (dd, 1H, $J = 15.7, 5.4$ Hz), 6.75 (bs, 1H), 7.19-7.35 (m, 5H), 7.59 (d, 1H, $J = 8.1$ Hz); Anal. ($\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_6\text{S}$) C, H, N.

Example 21 - Preparation of Compound 32: Ethyl-3-[N-(Benzylsulfonyl)-L-Phe-L-Gln]-E-Propenoate**Preparation of Intermediate Ethyl-3-[N-(Benzylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-Propenoate**

Ethyl-3-[L-Phe-L-(Tr-Gln)]-E-propenoate (0.250 g, 0.424 mmol) was dissolved in dry CH_2Cl_2 (7 mL) under argon and cooled to 0 °C. Triethylamine (0.118 mL, 0.847 mmol) and α -toluenesulfonyl chloride (0.162 g, 0.850 mmol) were added sequentially. After stirring for 45 min, the solvent was evaporated and the residue was purified by column chromatography (47% EtOAc in hexanes) to give the product as a white foam (0.154 g, 49%): IR (thin film) 3296, 1708, 1663, 1316, 1154 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.29 (t, 3H, $J = 7.2$ Hz), 1.59-1.72 (m, 1H), 1.91-2.03 (m, 1H), 2.31-2.37 (m, 2H), 2.82 (dd, 1H, $J = 13.7, 7.2$ Hz), 2.92 (dd, 1H, $J = 13.7, 7.2$ Hz), 3.78-3.87 (m, 1H), 3.90 (d, 1H, $J = 13.9$ Hz), 3.97 (d, 1H, $J = 13.9$ Hz), 4.17 (q, 2H, $J = 7.2$ Hz), 4.44-4.54 (m, 1H), 4.96 (d, 1H, $J = 7.8$ Hz), 5.59 (dd, 1H, $J = 15.7, 1.7$ Hz), 6.51 (d, 1H, $J = 7.5$ Hz), 6.63 (dd, 1H, $J = 15.7, 5.1$ Hz), 6.91 (s, 1H), 7.03-7.07 (m, 2H), 7.17-7.40 (m, 23H); Anal. ($\text{C}_{44}\text{H}_{43}\text{N}_3\text{O}_6\text{S}$) C, H, N.

Preparation of Product - Ethyl-3-[N-(Benzylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

This compound was prepared in 72% yield from ethyl-3-[N-(benzylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate using the procedure described in Example 20 for the preparation of ethyl-3-[N-(propylsulfonyl)-L-Phe-L-Gln]-E-propenoate: mp = 165-167 °C; IR (KBr) 3330, 3201, 1713, 1660, 1314 cm^{-1} ; ^1H NMR (acetone- d_6) δ 1.25 (t, 3H, $J = 7.2$ Hz), 1.72-1.99 (m, 2H), 2.22-2.30 (m, 2H), 2.96 (dd, 1H, $J = 13.5, 7.3$ Hz), 3.10 (dd, 1H, $J = 13.5, 7.0$ Hz), 4.03-4.22 (m, 5H), 4.51-4.62 (m, 1H), 5.72 (dd, 1H, $J = 15.6, 1.6$ Hz), 6.18 (bs, 1H),

6.33 (d, 1H, $J = 8.4$ Hz), 6.72 (bs, 1H), 6.73 (dd, 1H, $J = 15.6, 5.4$ Hz), 7.19-7.35 (m, 10H), 7.55 (d, 1H, $J = 8.1$ Hz); Anal. ($C_{23}H_{21}N_3O_6S$) C, H, N.

Example 22 - Preparation of Compound 33: Ethyl-3-[N-(Ethylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

Preparation of Intermediate Ethyl-3-[N-(Ethylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-Propenoate

This compound was prepared in 46% yield from ethyl-3-[L-Phe-L-(Tr-Gln)]-E-propenoate and ethanesulfonyl chloride using the procedure described in Example 21 for the preparation of ethyl-3-[N-(benzylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate. The material was purified by flash column chromatography (50% EtOAc in hexanes): IR (thin film) 3295, 1713, 1666, 1314, 1143 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 7.5$ Hz), 1.29 (t, 3H, $J = 7.2$ Hz), 1.68-1.81 (m, 1H), 1.95-2.06 (m, 1H), 2.33-2.43 (m, 2H), 2.45-2.58 (m, 1H), 2.59-2.72 (m, 1H), 2.86 (dd, 1H, $J = 13.7, 8.4$ Hz), 3.09 (dd, 1H, $J = 13.7, 5.6$ Hz), 3.96-4.04 (m, 1H), 4.19 (q, 2H, $J = 7.2$ Hz), 4.50-4.59 (m, 1H), 4.91 (bs, 1H), 5.72 (dd, 1H, $J = 15.9, 1.9$ Hz), 6.71 (dd, 1H, $J = 15.9, 5.3$ Hz), 6.87 (s, 1H), 6.96 (d, 1H, $J = 7.8$ Hz), 7.13-7.34 (m, 20H); Anal. ($C_{38}H_{44}N_6O_6S$) C, H, N.

Preparation of Product Ethyl-3-[N-(Ethylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

This compound was prepared in 82% yield from ethyl-3-[N-(ethylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate using the procedure described in Example 20 for the preparation of compound 31, ethyl-3-[N-(propylsulfonyl)-L-Phe-L-Gln]-E-propenoate: mp = 150-151 $^{\circ}C$; IR (KBr) 3284, 3225, 1713, 1655, 1314, 1138 cm^{-1} ; 1H NMR (acetone- d_6) δ 1.05 (t, 3H,

$J = 7.3$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz), 1.74-1.87 (m, 1H), 1.90-2.02 (m, 1H), 2.22-2.33 (m, 2H), 2.62-2.84 (m, 2H), 2.95 (dd, 1H, $J = 13.7, 8.7$ Hz), 3.15 (dd, 1H, $J = 13.7, 6.2$ Hz), 4.16 (q, 2H, $J = 7.2$ Hz), 4.13-4.23 (m, 1H), 4.54-4.64 (m, 1H), 5.78 (dd, 1H, $J = 15.9, 1.6$ Hz), 6.22 (bs, 1H), 6.34 (d, 1H, $J = 9.0$ Hz), 6.78 (bs, 1H), 6.78 (dd, 1H, $J = 15.9, 5.6$ Hz), 7.21-7.35 (m, 5H), 7.61 (d, 1H, $J = 8.1$ Hz); Anal. ($C_{20}H_{25}N_3O_6S$) C, H, N.

Example 23 - Preparation of Compound 34: Ethyl-3-[N-(Phenylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

Preparation of Intermediate Ethyl-3-[N-(Phenylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-Propenoate

This compound was prepared in 55% yield from ethyl-3-[L-Phe-L-(Tr-Gln)]-E-propenoate and benzenesulfonyl chloride using the procedure described in Example 21 for the preparation of ethyl-3-[N-(benzylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate. The material was purified by flash column chromatography (47% EtOAc in hexanes): IR (thin film) 3295, 1713, 1660, 1308, 1161 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.29 (t, 3H, $J = 7.2$ Hz), 1.59-1.72 (m, 1H), 1.83-1.95 (m, 1H), 2.12-2.33 (m, 2H), 2.82-2.94 (m, 2H), 3.82-3.91 (m, 1H), 4.18 (q, 2H, $J = 7.2$ Hz), 4.31-4.41 (m, 1H), 5.05 (d, 1H, $J = 7.8$ Hz), 5.67 (dd, 1H, $J = 15.7, 1.7$ Hz), 6.60 (dd, 1H, $J = 15.7, 5.4$ Hz), 6.72 (d, 1H, $J = 7.8$ Hz), 6.79 (s, 1H), 6.91-6.97 (m, 2H), 7.13-7.40 (m, 20H), 7.48-7.54 (m, 1H), 7.58-7.62 (m, 2H); Anal. ($C_{40}H_{40}N_3O_6S$) C, H, N.

Preparation of Product Ethyl-3-[N-(Phenylsulfonyl)-L-Phe-L-Gln]-E-Propenoate

This compound was prepared in 83% yield from ethyl-3-[N-(phenylsulfonyl)-L-Phe-L-(Tr-Gln)]-E-propenoate using the procedure described in Example 20 for the preparation of ethyl-3-[N-(propylsulfonyl)-L-Phe-L-Gln]-E-propenoate: mp = 173-175 °C; IR (KBr) 3284, 3201, 1708, 1660, 1314, 1161 cm⁻¹; ¹H NMR (acetone-*d*₆) δ 1.24 (t, 3H, *J* = 7.2 Hz), 1.59-1.85 (m, 2H), 2.07-2.19 (m, 2H), 2.85 (dd, 1H, *J* = 13.5, 7.6 Hz), 2.99 (dd, 1H, *J* = 13.5, 6.7 Hz), 4.03-4.16 (m, 1H), 4.13 (q, 2H, *J* = 7.2 Hz), 4.30-4.40 (m, 1H), 5.65 (dd, 1H, *J* = 15.7, 1.6 Hz), 6.21 (bs, 1H), 6.63 (dd, 1H, *J* = 15.7, 5.6 Hz), 6.74 (bs, 1H), 6.75 (d, 1H, *J* = 8.7 Hz), 7.07-7.29 (m, 5H), 7.42-7.61 (m, 4H), 7.67-7.80 (m, 2H); Anal. (C₂₄H₂₉N₃O₆S) C, H, N.

Example 24 - Preparation of Compound 35: Ethyl-3-[CBZ-L-Leu-L-(4-F-Phe)-L-Gln]-E-Propenoate**Preparation of Intermediate CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-Glutaminol)**

Using the procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminol), this intermediate was synthesized from CBZ-L-Leu and the free base of L-(4-F-Phe)-L-(Tr-glutaminol)HCl, in 68% yield as a white solid: IR (KBr) 3304, 3063, 2955, 1651, 1510, 1223, 1038, 752, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.79 (m, 6H), 1.34 (m, 2H), 1.46 (m, 2H), 1.72 (m, 1H), 2.25 (m, 2H), 2.80 (m, 1H), 2.99 (m, 1H), 3.16 (m, 1H), 3.26 (m, 1H), 3.64 (m, 1H), 3.95 (m, 1H), 4.47 (m, 1H), 4.66 (t, 1H, *J* = 5.5 Hz), 4.97 (d, 1H, *J* = 12.5 Hz), 5.02 (d, 1H, *J* = 12.5

Hz), 7.01 (t, 2H, $J = 8.8$ Hz), 7.15-7.37 (m, 22H), 7.42 (d, 1H, $J = 7.7$ Hz), 7.69 (d, 1H, $J = 8.5$ Hz), 7.87 (d, 1H, $J = 8$ Hz), 8.54 (s, 1H).

Preparation of Intermediate CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-Glutaminal)

Using the oxidation procedure described in Example 16 for the preparation of N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-glutaminal), this aldehyde was prepared from CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-glutaminol) in 92% yield as a white glassy solid, which was used immediately without further purification.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-Gln)]-E-Propenoate

Using the procedure described in Example 1 for the preparation of compound 12, ethyl-3-[CBZ-L-Leu-L-Phe-L-Met(sulfoxide)-E-propenoate, (carbethoxymethylene)triphenyl-phosphorane and CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-glutaminal) were stirred together in THF giving 0.37 g of the crude material contaminated with triphenylphosphine oxide which was subsequently used without further purification. A small amount (27 mg) was purified by flash column chromatography (MeOH/CHCl₃) for spectral analysis: ¹H NMR (DMSO-*d*₆) δ 0.79 (t, 6H, $J = 7.0$ Hz), 1.20 (t, 3H, $J = 7.0$ Hz), 1.23-1.82 (m, 5H), 2.25 (m, 2H), 2.85 (m, 1H), 2.95 (m, 1H), 3.96 (m, 1H), 4.10 (q, 2H, $J = 7.0$ Hz), 4.34 (m, 1H), 4.48 (m, 1H), 4.96 (d, 1H, $J = 13.0$ Hz), 5.02 (d, 1H, $J = 13.0$ Hz), 5.57 (d, 1H, $J = 15.0$ Hz), 6.67 (dd, 1H, $J = 15.0, 5.5$ Hz), 7.01 (t, 2H, $J = 9.0$ Hz), 7.13-

7.32 (m, 22H), 7.39 (d, 1H, $J = 8.0$ Hz), 7.99 (d, 1H, $J = 8.0$ Hz), 8.07 (d, 1H, $J = 8.0$ Hz), 8.58 (s, 1H).

Preparation of Product Ethyl-3-[CBZ-L-Leu-L-(4-F-Phe)-L-Gln]-E-Propenoate

This compound was prepared by the deprotection of ethyl-3-[CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-Gln)]-E-propenoate using the procedure describe in Example 32 for the preparation of compound 20, but in the absence of triisopropylsilane. The product was isolated as a white solid in 58% yield (2 steps from CBZ-L-Leu-L-(4-F-Phe)-L-(Tr-glutaminal). IR (KBr) 3439, 3293, 3067, 2961, 1692, 1643, 1539, 1227, 1045, 984, 835, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.80 (m, 6H), 1.21 (t, 3H, $J = 7.0$ Hz), 1.26 (m, 2H), 1.45 (m, 1H), 1.71 (m, 2H), 2.06 (t, 2H, $J = 7.5$ Hz), 2.81 (m, 1H), 2.94 (m, 1H), 3.97 (m, 1H), 4.10 (q, 2H, $J = 7.0$ Hz), 4.37 (m, 1H), 4.47 (m, 1H), 4.98 (d, 1H, $J = 12.5$ Hz), 5.04 (d, 1H, $J = 12.5$ Hz), 5.59 (d, 1H, $J = 16.0$ Hz), 6.68 (dd, 1H, $J = 16.0, 5.5$ Hz), 6.76 (bs, 1H), 7.01 (t, 2H, $J = 8.8$ Hz), 7.19-7.34 (m, 8H), 7.43 (d, 1H, $J = 8.0$ Hz), 8.05 (m, 2H); HRMS calcd for $\text{C}_{27}\text{H}_{41}\text{N}_4\text{O}_7\text{F} + \text{Cs}$ 745.2014 ($\text{M} + \text{Cs}$), found 745.2040 Anal. ($\text{C}_{27}\text{H}_{41}\text{N}_4\text{O}_7\text{F} \cdot 1.25 \text{H}_2\text{O}$) C, H, N.

Example 25 - Preparation of Compound 15: 3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoic Acid

Preparation of Intermediate *tert*-Butyl-3-[CBZ-L-Phe-L-(Tr-Gln)]-E-Propenoate

To 0.20 g (0.261 mmol) of CBZ-L-Leu-L-Phe-L-(Tr-glutaminal) was added 3 mL of dry THF. To this stirred solution was added (*tert*-butoxycarbonylmethylene)

triphenylphosphorane (0.098 g, 0.261 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was subjected to column chromatography with hexanes:EtOAc (6.5:3.5). The product was obtained in 69% yield as a white foam.

Preparation of Product 3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoic Acid

tert-Butyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate (0.157 g, 0.181 mmol) was dissolved in an excess of TFA, and 10 drops of water were added. The mixture was stirred at room temperature for 1 hour and evaporated to dryness. CCl₄ was added and the mixture was concentrated in vacuo to azeotrope any remaining water. The residue was slurried in Et₂O and the resulting white solid was filtered and dried to give 0.053 g (52%). mp = 219-220 °C (dec); IR (thin film); 2949, 1690, 3269, 1639 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.80 (dd, 6H, *J* = 9.0, 6.5 Hz), 1.23-1.38 (m, 2H), 1.41-1.56 (m, 1H), 1.61-1.79 (m, 2H), 2.0-2.1 (m, 2H), 2.84 (dd, 1H, *J* = 13.6, 8.9 Hz), 2.99 (dd, 1H, *J* = 13.5, 5.1 Hz), 3.91 (m, 1H), 4.32-4.41 (m, 1H), 4.44-4.54 (m, 1H), 5.01 (dd, 1H, *J* = 12.5, 12.1 Hz), 5.64 (d, 1H, *J* = 15.6 Hz), 6.64 (dd, 1H, *J* = 15.6, 5.6 Hz), 6.76 (bs, 1H), 7.14-7.38 (m, 11H), 7.43 (d, 1H, *J* = 7.5 Hz), 7.97 (d, 1H, *J* = 8.1 Hz), 8.04 (d, 1H, *J* = 8.1 Hz), 12.28 (bs, 1H).

Example 26 - Preparation of Compound 14: 3-(CBZ-L-Leu-L-Phe-DL-Gln)-E-Propenenitrile**Preparation of Intermediate 3-[BOC-DL-(Tr-Gln)]-E-Propenenitrile**

A solution of diethyl cyanomethylphosphonate (0.202 mL, 1.25 mmol) in dry THF (25 mL) was cooled to -78 °C. After dropwise addition of a solution of sodium bis(trimethylsilyl)amide in THF (1.0 M, 1.25 mL), the reaction solution was stirred for 20 minutes. A solution of BOC-L-(Tr-glutaminal) (0.590 g, 1.25 mmol) in dry THF (5 mL) was added dropwise, and, after stirring 50 minutes more, saturated aqueous NH₄Cl (4 mL) was added. The reaction mixture was allowed to warm to room temperature, and the THF was evaporated. Water (10 mL) was added to the residue, which was then extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (38% EtOAc in hexanes) to give the product (0.407 g, 66%) as a white foam: IR (thin film) 3321, 2225, 1694, 1515 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (s, 9H), 1.67-1.81 (m, 1H), 1.82-1.97 (m, 1H), 2.34-2.42 (m, 2H), 4.23 (bs, 1H), 4.97-5.06 (m, 1H), 5.39 (dd, 1H, *J* = 16.3, 1.6 Hz), 6.56 (dd, 1H, *J* = 16.3, 5.3 Hz), 6.77 (bs, 1H), 7.15-7.33 (m, 15H).

Preparation of Intermediate (CBZ-L-Leu-L-Phe)₂O

CBZ-L-Leu-L-Phe (1.5 g, 3.6 mmol) was dissolved in dry CH₂Cl₂ (25 mL) at room temperature under argon. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.697 g, 3.64 mmol) was added. The reaction solution was stirred for 20 hours, then diluted with CH₂Cl₂ (20 mL) and washed with water (2 x 20 mL). The combined organic

phases were dried over Na_2SO_4 and concentrated to give the anhydride product as a white semi-solid residue (1.18 g, 80%), which was used immediately in the next step of the reaction without further purification or analysis.

Preparation of Intermediate 3-[CBZ-L-Leu-L-Phe-DL-(Tr-Gln)]-E-Propenitrile

3-[BOC-DL-(Tr-Gln)]-E-Propenitrile (0.349 g, 0.704 mmol) was stirred in 2-propanol (9 mL) at room temperature. Perchloric acid (60%, 3.2 mL) was added dropwise. The resulting solution was stirred for 1 hour under an argon balloon, diluted with CH_2Cl_2 (100 mL), and poured into a solution of aqueous 1N NaOH/aqueous saturated NaHCO_3 (40 mL:70 mL). The phases were mixed and separated. The aqueous phase was washed again with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried over Na_2SO_4 and then concentrated to give the crude amine as a white solid (0.314 g), which was used without further purification. This amine was dissolved in acetone (15 mL) and added to the crude (CBZ-L-Leu-L-Phe) $_2\text{O}$ (1.18 g, 1.46 mmol) in a round bottom flask. The reaction solution was stirred at room temperature under an argon balloon. After stirring for 4.5 hours, the solvent was evaporated, and the residue was purified by flash column chromatography (30% EtOAc in hexanes, then 30% acetone in hexanes) to give the product (0.448 g, 81%) as a white foam: IR (thin film) 3298, 2226, 1672, 1519 cm^{-1} ; Anal. ($\text{C}_{44}\text{H}_{51}\text{N}_5\text{O}_5$) C, H, N.

Preparation of Product 3-(CBZ-L-Leu-L-Phe-DL-Gln)-E-Propenitrile

3-[CBZ-L-Leu-L-Phe-DL-(Tr-Gln)]-E-Propenitrile (0.381 g, 0.482 mmol) was dissolved in 1:1 CH_2Cl_2 /TFA (14 mL) under argon, giving a bright yellow solution. After

stirring for 30 minutes, the solvent was evaporated. CCl_4 (15 mL) was added, and the resulting solution was concentrated (3 times). The residue was triturated with Et_2O (8 mL) to give a white solid, which was collected by filtration. This solid was then stirred in acetonitrile (4 mL), collected by filtration, washed with acetonitrile (4 mL), washed with Et_2O (6 mL), and dried *in vacuo* (0.099 g, 38%): mp = 178-184 °C; IR (KBr) 3401, 3284, 2225, 1689, 1650, 1537 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) (2 diastereomers) δ 0.69 (d, 3H, $J = 5.3$ Hz), 0.73 (d, 3H, $J = 5.1$ Hz), 0.80 (d, 3H, $J = 6.6$ Hz), 0.83 (d, 3H, $J = 6.6$ Hz), 1.10-1.20 (m, 3H), 1.26-1.40 (m, 2H), 1.46-1.85 (m, 5H), 1.99-2.09 (m, 4H), 2.76 (dd, 1H, $J = 13.4$, 10.9 Hz), 2.83-2.99 (m, 2H), 3.10 (dd, 1H, $J = 13.6$, 4.3 Hz), 3.85-3.93 (m, 1H), 3.96-4.05 (m, 1H), 4.28-4.52 (m, 4H), 4.90-5.07 (m, 5H), 5.71 (d, 1H, $J = 16.4$ Hz), 6.68 (dd, 1H, $J = 16.4$, 4.6 Hz), 6.78 (s, 2H), 6.88 (dd, 1H, $J = 16.3$, 4.7 Hz), 7.16-7.37 (m, 22H), 7.41-7.47 (m, 2H), 7.96 (d, 1H, $J = 8.2$ Hz), 8.03-8.10 (m, 2H), 8.38 (d, 1H, $J = 8.2$ Hz); Anal. ($\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5$) C, H, N.

Example 27 - Preparation of Compound 6: N-Ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenamide

Preparation of Intermediate N-Ethyl-3-[BOC-L-(Tr-Gln)]-E-Propenamide

Isobutyl chloroformate (0.161 mL, 1.24 mmol) was added to a solution of 3-[BOC-L-(Tr-Gln)]-E-propenoic acid (0.639 g, 1.24 mmol) and 4-methylmorpholine (1.36 mL, 12.4 mmol) in CH_2Cl_2 at 0 °C. The resulting solution was stirred for 20 minutes at 0 °C, then ethylamine hydrochloride (0.810 g, 9.93 mmol) was added. The reaction mixture was warmed to 23 °C and was stirred for 24 hours, then was partitioned between water (100

mL) and a 9:1 mixture of CH_2Cl_2 and CH_3OH (2 x 100 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) provided an oil, which was triturated with EtOAc to afford a white solid. The solid was filtered, washed with EtOAc (2 x 20 mL), and was air-dried to give N-ethyl-3-[BOC-L-(Tr-Gln)]-E-propenamide (0.055 g, 8%): mp = 240 °C (dec); IR (thin film) 3255, 3085, 1715, 1665, 1612, 1529 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.15 (t, 3H, $J = 7.2$ Hz), 1.42 (s, 9H), 1.63-1.80 (m, 1H), 1.83-2.05 (m, 1H), 2.34-2.39 (m, 2H), 3.29-3.38 (m, 2H), 4.26 (s, br, 1H), 4.75 (s, br, 1H), 5.43 (s, br, 1H), 5.81 (d, 1H, $J = 15.4$ Hz), 6.65 (dd, 1H, $J = 15.4, 5.9$ Hz), 6.85 (s, 1H), 7.19-7.33 (m, 15H); Anal. ($\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_4$) C, H, N.

Preparation of Intermediate N-Ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenamide

N-Ethyl-3-[BOC-L-(Tr-Gln)]-E-propenamide (0.040 g, 0.074 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.030 g, 0.073 mmol) using the procedure described in Example 28 for the preparation of ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate to provide N-ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenamide (0.043 g, 70%) as a white solid: mp = 190 °C (dec); IR (thin film) 3283, 3067, 1693, 1642, 1535 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.83 (d, 3H, $J = 9.0$ Hz), 0.85 (d, 3H, $J = 9.0$ Hz), 1.14 (t, 2H, $J = 7.3$ Hz), 1.21-1.32 (m, 1H), 1.37-1.52 (m, 2H), 1.71-1.78 (m, 1H), 1.94-2.05 (m, 1H), 2.26 (t, 2H, $J = 7.3$ Hz), 2.91 (dd, 1H, $J = 13.8, 7.6$ Hz), 3.16 (dd, 1H, $J = 13.8, 6.2$ Hz), 3.26-3.35 (m, 2H), 3.94-4.01 (m, 1H), 4.53-4.55 (m, 2H), 4.89-4.94 (m, 3H), 5.56-

5.65 (m, 2H), 6.51 (d, 1H, $J = 8.1$ Hz), 6.60 (dd, 1H, $J = 15.1, 4.8$ Hz), 6.81 (d, 1H, $J = 8.4$ Hz), 7.02 (s, 1H), 7.10-7.36 (m, 26H); Anal. ($C_{31}H_{37}N_3O_6$) C, H, N.

Preparation of Products N-Ethyl-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenamide

Using the procedure described in Example 4 for the preparation of compound 3, N-ethyl-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenamide was deprotected to produce the product. mp = 230 °C (dec), $R_f = 0.28$ (10% MeOH in CH_2Cl_2); IR (KBr) 3404, 3075, 2943, 1692, 1643 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 0.78 (d, 3H, $J = 11.5$ Hz), 0.80 (d, 3H, $J = 11.5$ Hz), 1.02 (t, 3H, $J = 7.3$ Hz), 1.24-1.29 (m, 2H), 1.32-1.47 (m, 1H), 1.67-1.71 (m, 2H), 2.03-2.08 (m, 2H), 2.77-2.85 (m, 1H), 2.99-3.16 (m, 3H), 3.91-3.98 (m, 1H), 4.29-4.34 (m, 1H), 4.48-4.49 (m, 1H), 4.97 (d, 1H, $J = 12.5$ Hz), 5.04 (d, 1H, $J = 12.5$ Hz), 5.85 (d, 1H, $J = 15.3$ Hz), 6.43 (dd, 1H, $J = 15.4, 6.4$ Hz), 6.75 (s, 1H), 7.20 (bs, 7H), 7.30-7.34 (m, 4H), 7.41 (d, 1H, $J = 7.8$ Hz), 7.90 (d, 1H, $J = 7.8$ Hz), 7.97 (t, 1H, $J = 5.1$ Hz), 8.08 (d, 1H, $J = 8.1$ Hz); Anal. ($C_{31}H_{41}N_3O_6$) C, H, N.

Example 28 - Preparation of Compound 8: Ethyl-2-Fluoro-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Preparation of Intermediate Ethyl-2-Fluoro-3-[BOC-L-(Tr-Gln)]-E-Propenoate

Sodium bis(trimethylsilyl)amide (0.264 mL of a 1.0 M solution in THF, 0.264 mmol) was added to a solution of triethyl-2-fluoro-2-phosphonoacetate (0.054 mL, 0.266 mmol) in THF (10 mL) at -78 °C, and the resulting solution was stirred for 15 minutes at that temperature. BOC-L-(Tr-Glutaminal) (0.125 g, 0.264 mmol) in THF (10 mL) was

added via cannula, and the reaction mixture was stirred for 30 minutes at -78 °C then was partitioned between 0.5 M HCl (100 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 100 mL). The organic layers were dried over Na₂SO₄ and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided ethyl-2-fluoro-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.094 g, 63%) as a white foam: IR (thin film) 3324, 1724, 1670 cm⁻¹; ¹H NMR (CDCl₃) δ 1.33 (t, 3H, *J* = 7.2 Hz), 1.41 (s, 9H), 1.92-2.05 (m, 2H), 2.39 (t, 2H, *J* = 7.2 Hz), 4.28 (q, 2H, *J* = 7.2 Hz), 5.00 (bs, 2H), 5.74 (dd, 1H, *J* = 19.8, 8.6 Hz), 6.78 (s, 1H), 7.14-7.32 (m, 15H); Anal. (C₂₇H₃₇FN₂O₅) C, H, N.

Preparation of Intermediate Ethyl-2-Fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Propenoate.

A solution of HCl in 1,4-dioxane (4 mL of a 4.0 M solution, 16 mmol) was added to a solution of ethyl-2-fluoro-3-[BOC-L-(Tr-Gln)]-E-propenoate (0.310 g, 0.553 mmol) in the same solvent (4 mL) at 23 °C. The reaction mixture was stirred for 4 hours at 23 °C, then was concentrated. The resulting oil was dissolved in CH₂Cl₂, and CBZ-L-Leu-L-Phe (0.228 g, 0.553 mmol), 1-hydroxybenzotriazole hydrate (0.112 g, 0.828 mmol), 4-methylmorpholine (0.182 mL, 1.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.159 g, 0.829 mmol) were added sequentially. The reaction mixture was stirred for 12 hours at 23 °C, then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The organic layers were dried over Na₂SO₄ and were concentrated. Purification of the residue by flash column chromatography (5% CH₃OH/CH₂Cl₂) afforded ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate

(0.203 g, 43%) as a white foam: IR (thin film) 3394, 3066, 1724, 1647 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.84 (d, 3H, $J = 5.9$ Hz), 0.86 (d, 3H, $J = 6.2$ Hz), 1.32 (t, 3H, $J = 7.0$ Hz), 1.37-1.57 (m, 3H), 1.82-1.84 (m, 2H), 2.26-2.29 (m, 2H), 2.97-2.99 (m, 2H), 3.99-4.05 (m, 1H), 4.26 (q, 2H, $J = 7.0$ Hz), 4.46-4.49 (m, 1H), 4.95 (s, 2H), 5.06 (d, 1H, $J = 6.5$ Hz), 5.16-5.21 (m, 1H), 5.54 (dd, 1H, $J = 19.9, 9.7$ Hz), 6.55 (d, 1H, $J = 7.5$ Hz), 6.79 (d, 1H, $J = 7.5$ Hz), 6.99 (s, 1H), 7.07-7.42 (m, 25H); Anal. ($\text{C}_{51}\text{H}_{53}\text{FN}_4\text{O}_7$) C, H, N.

Preparation of Product Ethyl-2-Fluoro-3-(CBZ-L-Leu-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 4 for the preparation of compound 3, ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate was deprotected to produce the product. mp = 210-211 $^{\circ}\text{C}$, $R_f = 0.57$ (10% MeOH in CH_2Cl_2); IR (KBr) 3401, 3300, 3072, 2943, 1693, 1648 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.79 (d, 3H, $J = 10.9$ Hz), 0.82 (d, 3H, $J = 10.9$ Hz), 1.27 (t, 3H, $J = 7.2$ Hz), 1.32-1.49 (m, 3H), 1.65-1.80 (m, 2H), 1.99-2.06 (m, 2H), 2.78-2.96 (m, 2H), 3.96-4.01 (m, 1H), 4.25 (q, 2H, $J = 7.2$ Hz), 4.39-4.41 (m, 1H), 4.97-5.07 (m, 3H), 5.65 (dd, 1H, $J = 21.2, 10.0$ Hz), 6.74 (s, 1H), 7.16-7.30 (m, 7H), 7.32-7.34 (m, 4H), 7.44 (d, 1H, $J = 8.1$ Hz), 7.94 (d, 1H, $J = 8.1$ Hz), 8.03 (d, 1H, $J = 7.8$ Hz). Anal. ($\text{C}_{57}\text{H}_{64}\text{FN}_4\text{O}_7$) C, H, N.

Example 29 - Preparation of Compound 9: Methyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Sulfone**Preparation of Intermediate Methyl-(2-[BOC-L-(Tr-Gln)]-E-Vinyl) Sulfone**

Sodium bis(trimethylsilyl)amide (1.04 mL of a 1.0 M solution in THF, 1.04 mmol) was added to a solution of methanesulfonylmethyl-phosphinic acid diethyl ether (0.217 g, 0.943 mmol) in THF (30 mL) at -78 °C, and the resulting solution was stirred for 15 minutes at that temperature. BOC-L-(Tr-Glutaminal) (0.446 g, 0.944 mmol) in THF (15 mL) was added via cannula, and the reaction mixture was stirred for 30 minutes at -78 °C then was partitioned between 0.5 M HCl (100 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 100 mL). The organic layers were dried over Na₂SO₄ and were concentrated. Purification of the residue by flash column chromatography (40% hexanes in EtOAc) provided methyl-(2-[BOC-L-(Tr-Gln)]-E-vinyl) sulfone (0.359 g, 69%) as a white foam: IR (thin film) 3348, 1688, 1495 cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (s, 9H), 1.64-1.81 (m, 1H), 1.83-2.01 (m, 1H), 2.40 (t, 2H, *J* = 6.7 Hz), 2.91 (s, 3H), 4.35 (s, br, 1H), 5.01-5.04 (m, 1H), 6.42 (dd, 1H, *J* = 15.0, 1.7 Hz), 6.78 (s, 1H), 6.78 (dd, 1H, *J* = 15.0, 5.0 Hz), 7.18-7.33 (m, 15H); Anal. (C₃₁H₃₆N₂O₅S) C, H, N.

Preparation of Intermediate Methyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Vinyl) Sulfone.

Using the procedure described in Example 28 for the preparation of ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, methyl-(2-[BOC-L-(Tr-Gln)]-E-vinyl) sulfone (0.359 g, 0.654 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.270 g, 0.655 mmol) to provide methyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-vinyl)

sulfone (0.160 g, 29%) as a white foam: IR (thin film) 3296, 3061, 1649, 1529 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.84 (d, 3H, $J = 8.9$ Hz), 0.86 (d, 3H, $J = 8.9$ Hz), 1.24-1.36 (m, 2H), 1.42-1.55 (m, 2H), 1.72-1.75 (m, 1H), 1.96-1.99 (m, 1H), 2.23-2.32 (m, 2H), 2.85 (s, 3H), 2.97 (dd, 1H, $J = 13.8, 7.5$ Hz), 3.13 (dd, 1H, $J = 13.8, 6.1$ Hz), 3.92-3.99 (m, 1H), 4.43-4.56 (m, 2H), 4.88 (s, br, 2H), 4.95 (d, 1H, $J = 5.9$ Hz), 6.20 (d, 1H, $J = 14.9$ Hz), 6.47 (d, 1H, $J = 7.2$ Hz), 6.70 (dd, 1H, $J = 14.9, 4.4$ Hz), 6.98 (d, 1H, $J = 8.1$ Hz), 7.09-7.38 (m, 25H).

Preparation of Product - Methyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Sulfone

Using the procedure described in Example 4 for the preparation of compound 3, methyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-vinyl) sulfone was deprotected to produce the product. mp = 220 $^{\circ}\text{C}$ (dec), $R_f = 0.44$ (10% MeOH in CH_2Cl_2); IR (KBr) 3413, 3284, 3049, 2951, 1690, 1649 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.79 (d, 3H, $J = 10.6$ Hz), 0.81 (d, 3H, $J = 10.6$ Hz), 1.27-1.38 (m, 2H), 1.40-1.50 (m, 1H), 1.63-1.80 (m, 2H), 2.08 (t, 2H, $J = 7.5$ Hz), 2.82-2.89 (m, 1H), 2.96 (s, 3H), 2.98-3.04 (m, 1H), 3.94-3.99 (m, 1H), 4.45-4.53 (m, 2H), 4.98 (d, 1H, $J = 12.5$ Hz), 5.05 (d, 1H, $J = 12.5$ Hz), 6.38 (d, 1H, $J = 14.9$), 6.60 (dd, 1H, $J = 15.4, 5.1$ Hz), 6.78 (s, 1H), 7.17-7.31 (m, 7H), 7.34-7.36 (m, 4H), 7.43 (d, 1H, $J = 8.1$ Hz), 8.01 (d, 1H, $J = 8.1$ Hz), 8.13 (d, 1H, $J = 8.1$ Hz); Anal. ($\text{C}_{30}\text{H}_{40}\text{N}_4\text{O}_7\text{S}$) C, H, N.

Example 30 - Preparation of Compound 10: Phenyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Sulfone**Preparation of Intermediate Phenyl-(2-[BOC-L-(Tr-Gln)]-E-Vinyl) Sulfone**

Sodium bis(trimethylsilyl)amide (1.14 mL of a 1.0 M solution in THF, 1.14 mmol) was added to a solution of benzenesulfonylmethyl-phosphinic acid diethyl ether (0.304 g, 1.04 mmol) in THF (20 mL) at -78 °C, and the resulting solution was stirred for 15 minutes at that temperature. BOC-L-(Tr-Glutaminal) (0.491 g, 1.04 mmol) in THF (10 mL) was added via cannula, and the reaction mixture was stirred for 30 minutes at -78 °C then was partitioned between 0.5 M HCl (100 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 100 mL). The organic layers were dried over Na₂SO₄ and were concentrated. Purification of the residue by flash column chromatography (gradient elution, 30-40% EtOAc in hexanes) provided phenyl-(2-[BOC-L-(Tr-Gln)]-E-vinyl) sulfone (0.540 g, 85%) as a white foam: IR (thin film) 3347, 2250, 1688, 1493 cm⁻¹; ¹H NMR (CDCl₃) δ 1.37 (s, 9H), 1.73-1.81 (m, 1H), 1.83-1.94 (m, 1H), 2.38 (t, 2H, *J* = 6.7 Hz), 4.33 (s, br, 1H), 4.88-4.90 (m, 1H), 6.37 (dd, 1H, *J* = 15.3, 1.6 Hz), 6.79-6.86 (m, 2H), 7.17-7.32 (m, 15H), 7.49-7.54 (m, 2H), 7.58-7.63 (m, 1H), 7.83-7.87 (m, 2H); Anal. (C₂₆H₃₁N₂O₅S) C, H, N.

Preparation of Intermediate Phenyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Vinyl) Sulfone

Using the procedure described in Example 28 for the preparation of ethyl-2-fluoro-3-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-propenoate, phenyl-(2-[BOC-L-(Tr-Gln)]-E-vinyl) sulfone (0.205 g, 0.336 mmol) was deprotected and coupled with CBZ-L-Leu-L-Phe (0.138 g, 0.335 mmol) to provide phenyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-vinyl)

sulfone (0.100 g, 33%) as a white foam: IR (thin film) 3298, 3061, 1652, 1518 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.81 (d, 3H, $J = 6.9$ Hz), 0.83 (d, 3H, $J = 6.9$ Hz), 1.24-1.69 (m, 5H), 1.91 (s, br, 1H), 2.16-2.31 (m, 2H), 2.91 (dd, 1H, $J = 13.5, 7.5$ Hz), 3.05 (dd, 1H, $J = 13.5, 6.7$ Hz), 3.91-3.98 (m, 1H), 4.38-4.45 (m, 1H), 4.54 (s, br, 1H), 4.87 (s, br, 1H), 5.06 (d, 1H, $J = 6.2$ Hz), 6.12 (d, 1H, $J = 15.3$ Hz), 6.57 (d, 1H, $J = 7.2$ Hz), 6.75 (dd, 1H, $J = 15.3, 4.4$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 7.05 (d, 1H, $J = 7.2$ Hz), 7.10-7.37 (m, 24H), 7.40-7.62 (m, 3H), 7.79-7.82 (m, 2H); Anal. ($\text{C}_{36}\text{H}_{36}\text{N}_4\text{O}_7\text{S}$) C, H, N.

Preparation of Product - Phenyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Sulfone

Using the procedure described in Example 4 for the preparation of compound 3, phenyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-vinyl) sulfone was deprotected to produce the product. mp = 230 $^{\circ}\text{C}$ (dec), $R_f = 0.40$ (10% MeOH in CH_2Cl_2); IR (KBr) 3400, 3288, 3062, 2960, 1685, 1644 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.78 (d, 3H, $J = 10.6$ Hz), 0.81 (d, 3H, $J = 10.6$ Hz), 1.26-1.39 (m, 2H), 1.47-1.59 (m, 1H), 1.61-1.66 (m, 1H), 1.76-1.79 (m, 1H), 2.04 (t, 2H, $J = 7.0$ Hz), 2.77-2.96 (m, 2H), 3.95-4.00 (m, 1H), 4.43-4.45 (m, 2H), 4.96 (d, 1H, $J = 12.6$ Hz), 5.02 (d, 1H, $J = 12.6$ Hz), 6.33 (d, 1H, $J = 14.9$ Hz), 6.74-6.81 (m, 2H), 7.11-7.18 (m, 7H), 7.20-7.38 (m, 4H), 7.42 (d, 1H, $J = 7.8$ Hz), 7.65 (d, 2H, $J = 7.8$ Hz), 7.71 (d, 1H, $J = 7.5$ Hz), 7.82 (d, 2H, $J = 6.9$ Hz), 8.00 (d, 1H, $J = 7.8$ Hz), 8.09 (d, 1H, $J = 8.1$ Hz); Anal. ($\text{C}_{33}\text{H}_{32}\text{N}_4\text{O}_7\text{S}$) C, H, N.

Example 31 - Preparation of Compound 11: Ethyl-2-Fluoro-3-[BOC-L-(Cyanomethyl)-Ala]-E-Propenoate

Preparation of Intermediate BOC-L-Gln-OMe

To a solution of BOC-L-Gln (20 g, 81 mmol) in 50 mL of EtOAc and MeOH at 0 °C was added diazomethane in 250 mL of Et₂O with stirring. The resulting yellow solution was stirred at 0 °C for 5 minutes and then warmed up to room temperature and stirred for 20 minutes. Argon gas was then bubbled through the yellow reaction mixture to remove excess diazomethane. The crude product was concentrated and purified by crystallization from methyl-*tert*-butyl ether. Yield 100%. ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.96 (m, 1H), 2.21 (m, 1H), 2.36 (m, 2H), 3.76 (s, 3H), 4.34 (m, 1H), 5.32 (m, 1H), 5.44 (bs, 1H), 6.16 (bs, 1H). Anal. (C₁₁H₂₀N₂O₅) C, H, N.

Preparation of Intermediate BOC-L-(Cyanomethyl)-Ala-OMe

To a solution of BOC-L-Gln-OMe (10 g, 38 mmol) in 100 mL of pyridine at 0 °C was added 3.5 mL of POCl₃ dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was diluted with 100 mL EtOAc and washed with 1N HCl (2 x 50 mL). The organics were combined and dried over Na₂SO₄, concentrated to yield the crude product which was purified by flash column chromatography (1:4 EtOAc/hexane) to give the product in 67% yield. ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 2.03 (m, 1H), 2.27 (m, 1H), 2.46 (m, 2H), 3.80 (s, 3H), 4.38 (m, 1H), 5.20 (m, 1H).

Preparation of Intermediate BOC-L-(Cyanomethyl)-Alaninol

This compound was prepared in 84% yield from BOC-L-(cyanomethyl)-Ala-OMe using the procedure described in Example 2 for the preparation of CBZ-L-(N-Ac-amino)-alaninol. The compound was purified by flash column chromatography (50:50 EtOAc/hexane). ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.92 (m, 2H), 2.19 (m, 1H), 2.46 (m, 2H), 3.71 (m, 3H), 4.83 (m, 1H). Anal. (C₁₀H₁₁N₂O₃·0.4 H₂O) C, H, N.

Preparation of Intermediate BOC-L-(Cyanomethyl)-Alaninal

To a solution of oxalyl chloride (1.63 g, 12.57 mmol) in CH₂Cl₂ (30 mL) at -78 °C was added DMSO dropwise (2.01 g, 25.74 mmol). After the addition, the reaction was stirred for 5 minutes. A solution of BOC-L-(cyanomethyl)-alaninol (2.5 g, 11.7 mmol) in 20 mL was added at -78 °C with stirring. After 20 minutes, the reaction was treated with NEt₃ (8.15 mL, 58.5 mmol) and stirred for another 20 minutes. Water (40 mL) was added at -60 °C, and then the reaction was warmed up to room temperature. The water layer was separated and extracted with EtOAc (2 x 50 mL). The organic layers were combined and dried over MgSO₄, and then concentrated to give 2.1 g crude product which was purified by flash column chromatography using a gradient of 3:7 EtOAc/hexane to 5:5 EtOAc/hexane to give the aldehyde in 60% yield. ¹H NMR (CDCl₃) δ 1.37 (m, 3H), 1.42 (s, 9H), 1.46 (s, 9H), 1.91 (m, 1H), 2.55-2.30 (m, 3H), 4.25 (m, 1H), 5.27 (m, 1H), 9.63 (s, 1H).

Preparation of Intermediate Ethyl-2-Fluoro-3-[BOC-L-(Cyanomethyl)-Ala]-E-Propenoate

A solution of triethyl 2-fluoro-phosphonoacetate (0.31 g, 1.27 mmol) in 4 mL THF was cooled at -78 °C and then n-BuLi (0.56 mL of 2.5 M solution in hexanes, 1.39 mmol) was added. The resulting solution was stirred at -78 °C for 20 minutes, and then a solution of BOC-L-(cyanomethyl)-alaninal (0.124 g, 0.58 mmol) in 2 mL THF was added to the reaction mixture. The reaction was allowed to stir at -78 °C for 1 hour and then warmed up to room temperature and stirred overnight. Aqueous 6 N HCl (10 mL) was added to the reaction, and the organic layer was separated and washed with brine (2 x 10 mL) and concentrated. The crude product was purified by flash column chromatography (30:70 EtOAc/hexane) to give 0.07 g. product (55% yield). ¹H NMR (CDCl₃) δ 2.2-1.8 (m, 2H), 2.45 (m, 2H), 4.33 (m, 2H), 4.77 (m, 1H), 5.01 (m, 1H), 5.89 (m, 1H). Anal. (C₁₄H₂₁N₂O₄F·0.15 H₂O) C, H, N. MS calcd for C₁₄H₂₁N₂O₄F (M+Na), found 323.

Production of Product - Ethyl-2-Fluoro-3-[CBZ-L-Leu-L-Phe-L-(Cyanomethyl)-Ala]-E-Propenoate

A solution of ethyl-2-fluoro-3-[BOC-L-(cyanomethyl)-Ala]-E-propenoate (0.055 g, 0.18 mmol) in 1 mL CH₂Cl₂ was cooled to 0 °C, and 0.3 mL of TFA was added. The reaction was then warmed to room temperature, stirred for 3 hours, concentrated, and trace amounts of water were removed by toluene azeotrope. This crude product was dissolved in 2 mL DMF and a solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (0.12 g, 0.27 mmol), CBZ-L-Leu-L-Phe (0.11 g, 0.27 mmol), and Et₃N (0.075 mL, 0.54 mmol) was added at 0 °C, and the reaction was stirred for 4

hours. This reaction was diluted with saturated aqueous NaHCO₃ solution and extracted with EtOAc (3 x 15 mL). The organics layers were combined and dried with MgSO₄ and concentrated. The residue was purified by flash column chromatography using a solvent gradient of 1% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂, yielding the product in 37% (2-steps). Anal (C₃₂H₃₉N₄O₆F) C, H, N. HRMS calcd for C₃₂H₃₉N₄O₆F+Na 617.2751 (M + Na), found 617.2738.

Example 32 - Preparation of Compound 20: Diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Phosphonate

Preparation of Intermediate CBZ-L-(Tr-Gln)

CBZ-L-Gln (28.03 g, 100 mmol) was dissolved in 300 mL of glacial acetic acid. To this solution was added triphenylmethanol (26.83 g, 100 mmol), acetic anhydride (18.87 mL, 200 mmol), and 0.5 mL of sulfuric acid. The reaction was heated to 55 °C, stirring for one hour. After cooling to room temperature the mixture was concentrated under reduced pressure to one-third the original volume. Ice water was added, and the product extracted with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, and concentrated. The crude product was recrystallized from CH₂Cl₂/hexane, and the resulting crystals washed with Et₂O, yielding 37.27 g (71%) as a white solid: IR (KBr) 3418, 3295, 3059, 3032, 2949, 2515, 1699, 1628, 1539, 1504, 1447, 1418, 1341, 1242, 1209, 1061, 748, 696 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.71 (m, 1 H), 1.88 (m, 1 H), 2.38 (m, 2 H), 3.97 (m, 1 H), 5.04 (s, 2 H), 7.14-7.35 (m, 20H), 7.52 (d, 1 H, *J* = 7.7 Hz), 8.60 (s, 1 H).

Preparation of Intermediate CBZ-L-(Tr-Gln)OMe

CBZ-L-(Tr-Gln) (0.26 g, 0.5 mmol) was added to a stirring solution of 0.25 mL of acetyl chloride in 5 mL of MeOH, and stirring was continued at room temperature for 1 hour. The solvent was removed in vacuo, and the residue dissolved in 100 ml CH₂Cl₂. The organic layer was washed with water, saturated NaHCO₃, and brine followed by drying over Na₂SO₄. The crude product was purified on a short flash silica gel column, eluting with 20% EtOAc/hexane. The product (0.23 g, 84%) was obtained as a white solid: IR (KBr) 3405, 3277, 3057, 3034, 2953, 1724, 1643, 1532, 1493, 1447, 1207, 1042, 750, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.16 (t, 1 H, *J* = 7.0 Hz), 1.77 (m, 1 H), 1.97 (m, 1H), 3.61 (s, 3H), 4.99 (m, 1H), 5.03 (s, 2H), 7.02-7.55 (m, 20H), 7.69 (d, 1H, *J* = 7.7 Hz), 8.59 (s, 1H). Anal. (C₂₇H₃₁N₃O₅) C, H, N.

Preparation of Intermediate CBZ-L-(Tr-Glutaminol)

CBZ-L-(Tr-Gln)OMe (1.50 g, 2.79 mmol) was dissolved in 20 mL of THF and 10 mL of EtOH. LiCl (0.24 g, 5.6 mmol) was added, and the mixture stirred for 10 minutes until all solids had dissolved. NaBH₄ (0.21 g, 5.6 mmol) was added, and the reaction stirred overnight at room temperature. The solvents were removed in vacuo, the residue taken up in water, and the pH was adjusted to 2-3 with 10% HCl. The product was extracted with EtOAc, and the organic layer was washed with water and brine before drying over MgSO₄. The crude product was purified on a short flash silica gel column, eluting with an increasing gradient of EtOAc/benzene, yielding 1.02 g (72%) of a white glassy solid: IR (KBr) 3408, 3318, 3057, 3032, 2947, 1699, 1674, 1516, 1447, 1240, 1059, 752, 698 cm⁻¹;

^1H NMR ($\text{DMSO}-d_6$) δ 1.40 (m, 1H), 1.72 (m, 1H), 2.26 (m, 2H), 3.17-3.50 (m, 3H), 4.64 (t, 1H, $J = 5.0$ Hz), 5.00 (s, 2H), 7.00-7.40 (m, 20H), 6.96 (d, 1H, $J = 8.5$ Hz), 8.54 (s, 1H). Anal. ($\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$) C, H, N.

Preparation of Intermediate L-(Tr-Glutaminol)

This amino alcohol was prepared from CBZ-L-(Tr-glutaminol) in 98% yield using the procedure described in Example 2 for the preparation of L-(N-Ac-amino)-alaninol. IR (KBr) 3255, 3057, 3016, 2916, 1642, 1527, 1491, 1446, 1057, 1036, 750, 700, 636 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.29 (m, 1H), 1.53 (m, 1H), 2.29 (m, 2H), 3.08 (m, 1H), 3.18 (m, 2H), 3.38 (bs, 2H), 4.43 (bs, 1H), 7.14-7.28 (m, 15H), 8.62 (s, 1H). Anal. ($\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5$) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(Tr-Glutaminol)

Using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninol, this derivative was synthesized from CBZ-L-Leu-L-Phe and L-Tr-glutaminol in 62% yield as a white solid: IR (KBr) 3302, 3057, 3032, 2951, 1954, 1885, 1657, 1520, 1238, 1045, 746, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.79 (t, 6H, $J = 7.0$ Hz), 1.30 (m, 2H), 1.44 (m, 2H), 1.75 (m, 1H), 2.22 (m, 2H), 2.82 (m, 1H), 2.97 (m, 1H), 3.14 (m, 1H), 3.25 (m, 1H), 3.63 (m, 1H), 3.95 (m, 1H), 4.48 (m, 1H), 4.65 (t, 1H, $J = 5.0$ Hz), 4.96 (d, 1H, $J = 13.0$ Hz), 5.02 (d, 1H, $J = 13.0$ Hz), 7.07-7.33 (m, 25H), 7.42 (d, 1H, $J = 8.0$ Hz), 7.66 (d, 1H, $J = 8.5$ Hz), 7.86 (d, 1H, $J = 8.0$ Hz), 8.52 (s, 1H). Anal. ($\text{C}_{61}\text{H}_{82}\text{N}_{10}\text{O}_{10} \cdot 0.5 \text{H}_2\text{O}$) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Phe-L-(Tr-Glutaminal)

Using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninal, this aldehyde was synthesized from CBZ-L-Leu-L-Phe-L-(Tr-glutaminol) in 92% yield as a white glassy solid, which was used immediately. ^1H NMR (DMSO- d_6) δ 0.79 (t, 6H, $J = 7.0$ Hz), 1.00-1.98 (m, 5H), 2.27 (m, 2H), 2.84 (m, 1H), 3.02 (m, 1H), 3.98 (m, 2H), 4.58 (m, 1H), 4.99 (s, 2H), 7.14-7.32 (m, 25H), 7.39 (d, 1H, $J = 8.0$ Hz), 7.97 (d, 1H, $J = 8.5$ Hz), 8.38 (d, 1H, $J = 8.0$ Hz), 8.60 (s, 1H), 9.20 (s, 1H).

Preparation of Intermediate Diethyl-(2-[CBZ-L-Leu-L-Phe-L-(Tr-Gln)]-E-Vinyl) Phosphonate

Tetraethyl methylenediphosphonate (0.21 mL, 0.86 mmol) was dissolved in 10 mL of THF and cooled to 0 °C. Potassium bis(trimethylsilyl)amide (0.5 M in toluene) was added dropwise via syringe, and the reaction stirred at 0 °C for 30 minutes. After cooling the reaction to -30 °C a solution of CBZ-L-Leu-L-Phe-L-(Tr-glutaminol) (0.63 g, 0.82 mmol) in 6 mL of THF was added dropwise. The reaction was allowed to warm slowly to room temperature and stirred overnight. The solvent was removed by evaporation, and the crude product was purified by flash column chromatography eluting with 1% (saturated anhydrous NH_3/MeOH)/ CHCl_3 to afford 0.50 g (68%) of a white crystalline solid: IR (KBr) 3289, 3059, 3032, 2957, 1667, 1532, 1447, 1246, 1026, 968, 748, 698 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 0.78 (t, 6H, $J = 7.0$ Hz), 1.20 (m, 6H), 1.15-1.78 (m, 5H), 2.25 (m, 2H), 2.85 (m, 1H), 2.97 (m, 1H), 3.86-4.07 (m, 5H), 4.32 (m, 1H), 4.51 (m, 1H), 4.95 (d, 1H, $J = 13.0$ Hz), 5.02 (d, 1H, $J = 13.0$ Hz), 5.52 (t, 1H, $J = 19.0$ Hz), 6.48 (t, 1H, $J = 19.0$ Hz), 7.07-

7.32 (m, 25H), 7.41 (d, 1H, $J = 8.0$ Hz), 7.97 (d, 1H, $J = 8.5$ Hz), 8.05 (d, 1H, $J = 8.0$ Hz), 8.59 (s, 1H); MS (M+H) 901, (M-H) 899. Anal. ($C_{37}H_{41}N_4O_4P \cdot 2.5 H_2O$) C, H, N.

Preparation of Product Diethyl-[2-(CBZ-L-Leu-L-Phe-L-Gln)-E-Vinyl] Phosphonate

The protected amide diethyl-[2-(CBZ-L-Leu-L-Phe-L-Tr-Gln)-E-vinyl] phosphonate (0.469 g, 0.52 mmol) was dissolved in 10 mL of CH_2Cl_2 . Triisopropylsilane (0.52 mL) was added as a triphenylmethyl cation scavenger. TFA (1.0 mL) was added, and the reaction was stirred overnight at room temperature. The reaction was poured into EtOAc and washed with saturated $NaHCO_3$ solution. The organic layer was separated and washed with water and brine followed by drying over $MgSO_4$. The product was purified by flash column chromatography eluting with 2-3% MeOH/ $CHCl_3$ to give in 67% yield of a white solid: IR (KBr) 3291, 3063, 2955, 1647, 1541, 1236, 1026, 968, 746, 698 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 0.79 (m, 6H), 1.21 (t, 6H, $J = 7.0$ Hz), 1.28 (m, 2H), 1.52 (m, 1H), 1.63 (m, 1H), 1.75 (m, 1H), 2.06 (m, 2H), 2.85 (m, 1H), 3.00 (m, 1H), 3.92 (m, 5H), 4.34 (m, 1H), 4.50 (m, 1H), 4.97 (d, 1H, $J = 13.0$ Hz), 5.04 (d, 1H, $J = 13.0$ Hz), 5.54 (t, 1H, $J = 19.0$ Hz), 6.49 (t, 1H, $J = 19.0$ Hz), 6.77 (bs, 1H), 7.15-7.34 (m, 11H), 7.44 (d, 1H, $J = 8.0$ Hz), 8.00 (d, 1H, $J = 8.5$ Hz), 8.03 (d, 1H, $J = 8.0$ Hz); HRMS calcd for $C_{37}H_{41}N_4O_4P$ 659.3210 (M+H), found 659.3223. Anal. ($C_{37}H_{41}N_4O_4P$) C, H, N.

Example 33 - Preparation of Compound 29: Ethyl-3-[N-(1-Tr-4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-Gln]-E-Propenoate**Preparation of Product - Ethyl-3-[N-(1-Tr-4-Methoxyindole-2-Carbonyl)-L-(4-Cl-Phe)-L-Gln]-E-Propenoate**

This compound was prepared by the deprotection of ethyl-3-[N-(4-methoxyindole-2-carbonyl)-L-(4-Cl-Phe)-L-(Tr-Gln)]-E-propenoate, using the procedure described in Example 32 for the preparation of compound 20, but in the absence of triisopropylsilane.

¹H NMR (DMSO-*d*₆) δ 1.20 (t, 3H, *J* = 7.0 Hz), 1.74 (m, 2H), 2.03 (t, 2H, *J* = 8.0 Hz), 2.94 (m, 2H), 3.89 (s, 3H), 4.11 (q, 2H, *J* = 7.0 Hz), 4.46 (m, 1H), 4.60 (m, 1H), 5.70 (d, 1H, *J* = 15.0 Hz), 6.54 (d, 1H, *J* = 7.8 Hz), 6.70 (dd, 1H, *J* = 15.0, 5.7 Hz), 6.75 (bs, 1H), 6.87 (d, 1H, *J* = 8.5 Hz), 7.06 (m, 5H), 7.31 (m, 18H), 7.72 (bs, 1H), 8.26 (d, 1H, *J* = 8.2 Hz), 8.61 (d, 1H, *J* = 8.1 Hz); HRMS calcd for C₄₁H₄₆N₄O₆Cl+Cs 929.2082 (M+Cs), found 929.2078
 Anal. (C₄₁H₄₆N₄O₆Cl·1.0 H₂O) C, H, N.

Example 34- Preparation of Compound 167: Ethyl-3-[Ethylthiocarbonyl-L-α-(t-Butyl-Gly)-L-Phe-L-Gln]-E-Propenoate.**Preparation of Intermediate CBZ-L-Phe-L-(Tr-Glutaminol).**

Using the procedure described in Example 16 for the preparation of BOC-L-(4-Cl-Phe)-(Tr-glutaminol), CBZ-L-Phe-L-(Tr-glutaminol) was synthesized from CBZ-L-Phe and L-(Tr-glutaminol) in 67% yield as a white glassy solid: IR (KBr) 3304, 3059, 3030, 2936, 1956, 1887, 1809, 1659, 1495, 1446, 1246, 1036, 750, 698 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.47 (m, 1H), 1.72 (m, 1H), 2.26 (m, 2H), 2.75 (m, 1H), 2.94 (m, 1H), 3.18 (m, 1H), 3.26 (m, 1H), 3.66 (m, 1H), 4.21 (m, 1H), 4.66 (m, 1H), 4.90 (m, 2H),

7.15-7.30 (m, 25H), 7.43 (d, 1H, $J = 8.5$ Hz), 7.72 (d, 1H, $J = 9.0$ Hz), 8.49 (s, 1H). Anal. ($C_{41}H_{41}N_3O_5 \cdot 1.0 H_2O$) C, H, N.

Preparation of Intermediate L-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 2 for the preparation of L-(N-Ac-amino)-alaninol, L-Phe-L-(Tr-Glutaminol) was synthesized from CBZ-L-Phe-L-(Tr-glutaminol) in quantitative yield as a white glassy solid: IR (KBr) 3293, 3061, 3026, 2938, 2361, 1669, 1495, 1446, 752, 700 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 1.46 (m, 1H), 1.78 (m, 1H), 2.28 (m, 2H), 3.10 (m, 2H), 3.21 (m, 1H), 3.25 (m, 1H), 3.62 (m, 1H), 3.86 (t, 1H, $J = 6.0$ Hz), 4.72 (m, 1H), 7.10-7.32 (m, 20H), 8.14 (d, 1H, $J = 8.0$ Hz), 8.53 (s, 1H). MS calcd for $C_{33}H_{33}N_3O_3 + H$ 522, found 522. Anal. ($C_{33}H_{33}N_3O_3 \cdot 0.55 CH_2Cl_2$) C, H, N.

Preparation of Intermediate BOC-L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-Glutaminol).

L-Phe-L-(Tr-Glutaminol) (0.65 g, 1.25 mmol) was dissolved in 5 mL of DMF. Diisopropylethylamine (0.44 mL, 2.5 mmol) was added, followed by 0.29 g (1.25 mmol) of BOC-L- α -t-butylglycine. The reaction was cooled to 0 °C and HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.48 g, 1.25 mmol) was added. The reaction mixture was allowed to warm to rt at which time the DMF was removed in vacuo. The residue was dissolved with EtOAc, and the organic phase washed consecutively with 10% aq HCl solution, sat. $NaHCO_3$ solution, H_2O , and brine. The solvent was dried ($MgSO_4$) and filtered, and the residue purified by flash silica gel

chromatography using a gradient solvent system (0-1.5% MeOH/CHCl₃) to give 0.78 g (85%) of a white amorphous solid: IR (KBr) 3314, 2967, 1657, 1495, 1368, 1246, 1169, 1057, 752, 700 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.78 (s, 9H), 1.37 (s, 10H), 1.72 (m, 1H), 2.23 (m, 2H), 2.80 (m, 1H), 2.92 (m, 1H), 3.08 (m, 1H), 3.21 (m, 1H), 3.60 (m, 1H), 3.83 (d, 1H, *J* = 9.0 Hz), 4.55 (m, 1H), 4.59 (t, 1H, *J* = 5.5 Hz), 6.42 (d, 1H, *J* = 9.0 Hz), 7.14-7.28 (m, 20H), 7.67 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 8.45 (s, 1H); Anal. (C₄₄H₅₄N₄O₆•1.0 H₂O) C, H, N.

Preparation of Intermediate L-α-(t-Butyl-Gly)-L-Phe-L-(Tr-Glutaminol) Hydrochloride Salt.

BOC-L-α-(t-butyl-Gly)-L-Phe-L-(Tr-glutaminol) (0.745 g, 1.01 mmol) was dissolved in 2 mL of CH₂Cl₂ followed by 20 mL of Et₂O. Dry HCl gas was carefully bubbled into the solution until the white solid stopped precipitating. The reaction mixture was concentrated, and 2-3 mL of THF was added which redissolved the white solids. Thin layer chromatography indicated that the reaction went to completion. The THF was removed under vacuum and white solids were washed thoroughly with an excess of Et₂O and dried to yield L-α-(t-butyl-Gly)-L-Phe-L-(Tr-glutaminol) hydrochloride salt in 95% yield. IR(KBr) 3258, 3057, 2967, 1661, 1520, 700 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.95 (s, 9H), 1.44 (m, 1H), 1.72 (m, 1H), 2.13 (m, 1H), 2.25 (m, 1H), 2.97 (m, 2H), 3.06 (m, 1H), 3.15 (m, 1H), 3.60 (m, 2H), 4.25 (bs, 1H), 4.55 (m, 1H), 7.13-7.27 (m, 20H), 7.89 (d, 1H, *J* = 8.0 Hz), 8.13 (bs, 2H), 8.49 (s, 1H), 8.61 (d, 1H, *J* = 7.7 Hz); Anal. (C₃₉H₄₆N₄O₄•HCl•1.0 H₂O) C, H, N.

Preparation of Intermediate Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-Glutaminol).

L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-glutaminol) hydrochloride salt (0.61 g, 0.91 mmol) was dissolved in 9 mL of CH₂Cl₂. Triethylamine (0.26 mL, 1.87 mmol) was added, followed by the addition of 0.097 g (0.91 mL) of ethyl chlorothioformate. After stirring for five minutes at rt, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with a gradient solvent system (0-2% MeOH/CHCl₃) to give 0.47 g (71%) of a white amorphous solid: IR(KBr) 3300, 3059, 3026, 2967, 1649, 1493, 1194, 750, 698 cm⁻¹; ¹H NMR (DMSO-d₆) 0.83 δ (s, 9H), 1.16 (t, 3H, J = 7.0 Hz), 1.42 (m, 1H), 1.69 (m, 1H), 2.23 (m, 2H), 2.75 (q, 2H, J = 7.0 Hz), 2.80 (m, 1H), 2.96 (m, 1H), 3.08 (m, 1H), 3.18 (m, 1H), 3.62 (m, 1H), 4.25 (d, 1H, J = 9.0 Hz), 4.48 (m, 1H), 5.75 (t, 1H, J = 5.0 Hz), 7.10-7.28 (m, 20H), 7.60 (d, 1H, J = 8.5 Hz), 7.93 (d, 1H, J = 9.0 Hz), 8.09 (d, 1H, J = 7.7 Hz), 8.48 (s, 1H); Anal. (C₄₂H₅₀N₄O₅S) C, H, N.

Preparation of Intermediate Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-Glutaminal).

Using the general procedure described in Example 1 for the preparation of CBZ-L-L-Leu-L-Phe-L-methioninal (sulfoxide), ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminal) was synthesized from ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminol) in quantitative yield and isolated as a white amorphous solid and

used without further purification: ^1H NMR ($\text{DMSO}-d_6$) δ 0.83 (s, 9H), 1.16 (t, 3H, $J = 7.0$ Hz), 1.55 (m, 1H), 1.86 (m, 1H), 2.26 (m, 2H), 2.74 (q, 2H, $J = 7.0$ Hz), 2.85 (m, 1H), 2.98 (m, 1H), 3.90 (m, 1H), 4.25 (d, 1H, $J = 9.0$ Hz), 4.59 (m, 1H), 7.14-7.28 (m, 20H), 7.93 (d, 1H, $J = 9.0$ Hz), 8.18 (d, 1H, $J = 7.7$ Hz), 8.38 (d, 1H, $J = 6.6$ Hz), 8.52 (s, 1H), 9.13 (s, 1H).

Preparation of Intermediate Ethyl-3-[Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-*Met* (sulfoxide)]-E-propenoate, ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-propenoate was synthesized from ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminal) (0.22 g, 0.30 mmol) to give 0.28 g of material contaminated with triphenylphosphine oxide which was used without further purification: white amorphous solid: ^1H NMR ($\text{DMSO}-d_6$) δ 0.83 (s, 9H), 1.21 (m, 6H), 1.60 (m, 2H), 2.25 (m, 2H), 2.74 (q, 2H, $J = 7.0$ Hz), 2.82 (m, 1H), 2.92 (m, 1H), 4.09 (q, 2H, $J = 7.0$ Hz), 4.25 (d, 1H, $J = 9.0$ Hz), 4.34 (m, 1H), 4.52 (m, 1H), 5.53 (d, 1H, $J = 15.5$ Hz), 6.63 (dd, 1H, $J = 15.5, 5.5$ Hz), 7.08-7.28 (m, 20H), 7.93 (d, 1H, $J = 9.0$ Hz), 8.07 (d, 1H, $J = 7.7$ Hz), 8.16 (d, 1H, $J = 7.7$ Hz), 8.51 (s, 1H).

Preparation of Product - Ethyl-3-[Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-Gln]-E-Propenoate.

Ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-propenoate, impure with triphenylphosphine oxide (0.28 g), was dissolved in 6 mL of CH_2Cl_2 . TFA (0.6 mL) was added, and the reaction stirred at rt for 4 hours. The reaction was poured into an EtOAc/ sat. NaHCO_3 solution and agitated until white solids began to precipitate out of the organic layer. The aqueous layer was separated, and the solids were filtered and washed with EtOAc to give 0.074 g of a white solid (45% yield from the ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminal); 2 steps): IR(KBr) 3302, 2967, 1645, 1541, 1196 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 0.83 (s, 9H), 1.18 (m, 6H), 1.67 (m, 2H), 2.03 (m, 2H), 2.75 (q, 2H, $J = 7.0$ Hz), 2.86 (m, 1H), 2.93 (m, 1H), 4.10 (q, 2H, $J = 7.0$ Hz), 4.25 (d, 1H, $J = 9.0$ Hz), 4.35 (m, 1H), 4.49 (m, 1H), 5.55 (d, 1H, $J = 15.5$ Hz), 6.64 (dd, 1H, $J = 15.5, 5.5$ Hz), 6.73 (bs), 7.19 (m, 6H), 7.97 (d, 1H, $J = 8.5$ Hz), 8.07 (d, 1H, $J = 8.0$ Hz), 8.15 (d, 1H, $J = 7.7$ Hz); HRMS calcd for $\text{C}_{27}\text{H}_{40}\text{N}_4\text{O}_6\text{S} + \text{Cs}$ 681.1723, found 681.1738. Anal. ($\text{C}_{27}\text{H}_{40}\text{N}_4\text{O}_6\text{S}$) C, H, N.

Example 35 - Preparation of Compound 168: Ethyl-2-Methyl-3-[Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-Gln]-E-Propenoate.

Preparation of Intermediate Ethyl-2-Methyl-3-[Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-Met (sulfoxide)]-E-propenoate, ethyl-2-methyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-propenoate was

synthesized from ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminal) (0.22 g, 0.30 mmol) and (carbethoxyethylidene)triphenylphosphorane (0.14 g, 0.37 mmol). The product (0.31 g), a white amorphous solid, contaminated with triphenylphosphine oxide, was isolated after column chromatography and used without further purification: ^1H NMR (DMSO- d_6) δ 0.83 (s, 9H), 1.18 (m, 6H), 1.54 (m, 1H), 1.66 (m, 1H), 1.73 (s, 3H), 2.21 (m, 2H), 2.75 (q, 2H, $J = 7.0$ Hz), 2.80 (m, 1H), 2.88 (m, 1H), 4.12 (q, 2H, $J = 7.0$ Hz), 4.24 (d, 1H, $J = 9.0$ Hz), 4.44 (m, 2H), 6.27 (d, 1H, $J = 8.5$ Hz), 7.13-7.27 (m, 20H), 7.95 (d, 1H, $J = 9.0$ Hz), 8.03 (d, 1H, $J = 8.0$ Hz), 8.09 (d, 1H, $J = 7.0$ Hz), 8.51 (s, 1H).

Preparation of Product - Ethyl-2-Methyl-3-[Ethylthiocarbonyl-L- α -(t-Butyl-Gly)-L-Phe-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-2-methyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate was synthesized from ethyl-2-methyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-Gln)]-E-propenoate and isolated as a white glassy solid after purification by column chromatography on silica gel using a gradient solvent system (0-2% MeOH/ CHCl_3) (58% yield; two steps from ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-(Tr-glutaminal): IR (KBr) 3302, 2967, 1647, 1541, 1261, 1202 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 0.83 (s, 9H), 1.18 (m, 6H), 1.65 (m, 1H), 1.69 (m, 1H), 1.77 (s, 3H), 2.00 (m, 2H), 2.75 (q, 2H, $J = 7.0$ Hz), 2.86 (m, 2H), 4.12 (q, 2H, $J = 7.0$ Hz), 4.24 (d, 1H, $J = 9.0$ Hz), 4.42 (m, 2H), 6.26 (d, 1H, $J = 8.5$ Hz), 6.71 (bs, 1H), 7.15 (m, 6H), 7.96 (d, 1H, $J = 9.0$ Hz), 8.03 (d, 1H, $J = 7.7$ Hz),

8.07 (d, 1H, $J = 7.0$ Hz); HRMS calcd for $C_{28}H_{42}N_4O_6S + Cs$ 695.1879, found 695.1864.

Anal. ($C_{28}H_{42}N_4O_6S \cdot 0.2 CHCl_3$) C, H, N.

Example 36 - Preparation of Compound 178:

Ethyl-3-[Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-Gln]-E-Propenoate.

Preparation of Intermediate BOC-L-(S-Me-Pen)-L-Phe-L-(Tr-Glutaminol).

L-Phe-L-(Tr-Glutaminol) (0.64 g, 1.25 mmol) was dissolved in 4 mL of DMF. Diisopropylethylamine (0.43 mL, 2.46 mmol) was added, followed by BOC-S-methyl-L-penicillamine (0.32 g, 1.25 mmol; generated from the BOC-S-methyl-L-penicillamine dicyclohexylammonium salt (Sigma Chemical, St. Louis, MO) and aq HCl / EtOEt extraction and drying by benzene azeotrope). The solution was cooled to 0 °C, HATU (O-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.468 g, 1.25 mmol) was added, and the reaction mixture was allowed to warm to rt. The DMF was then removed in vacuo, the residue was dissolved with EtOAc, and the organic phase was washed consecutively with 10% HCl solution, sat $NaHCO_3$, H_2O , and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give a residue which was purified by column chromatography on silica gel using a gradient solvent system (0-1% MeOH/ $CHCl_3$) to yield 0.76 g (81%) of a white amorphous solid: IR (KBr) 3308, 2937, 1695, 1677, 1506, 1493, 1448, 1367, 1246, 1165, 700 cm^{-1} ; 1H NMR ($DMSO-d_6$) δ 1.07 (s, 3H), 1.19 (s, 3H), 1.37 (s, 9H), 1.66-1.75 (m, 2H), 1.94 (s, 3H), 2.19-2.25 (m, 2H), 2.78-2.83 (m, 1H), 2.95-3.01 (m, 1H), 3.06-3.12 (m, 1H), 3.19-3.23 (m, 1H), 3.62-3.65 (m, 1H), 4.12 (d, 1H, $J = 3.0$ Hz), 4.48-4.55 (m, 1H),

4.59-4.62 (m, 1H), 6.50 (d, 1H, $J = 9.0$ Hz), 7.14-7.28 (m, 20H), 7.62 (d, 1H, $J = 6.0$ Hz), 8.21 (d, 1H, $J = 6.0$ Hz), 8.47 (s, 1H). MS calcd for $C_{44}H_{54}N_4O_6S+H$ 767, found 767.

Preparation of Intermediate L-(S-Me-Pen)-L-Phe-L-(Tr-Glutaminol) Hydrochloride Salt.

To a solution of BOC-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol) (0.69 g, 0.91 mmol) in 6 mL of 1,4-dioxane was added 4 mL of 4M HCl/1,4-dioxane. The reaction mixture was stirred at rt for 3 h under an argon atmosphere. At this time the solvent was removed in vacuo to give 0.61 g (97%) of a white solid which was used without further purification: IR (KBr) 3313, 3057, 2926, 1664, 1493, 1448, 750, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.18 (s, 3H), 1.39 (s, 3H), 1.66-1.78 (m, 2H), 2.01 (s, 3H), 2.06-2.15 (m, 1H), 2.27-2.39 (m, 1H), 2.83-3.08 (m, 2H), 3.14-3.29 (m, 2H), 3.33-3.40 (m, 3H), 3.59-3.68 (m, 1H), 3.84-3.89 (m, 1H), 7.13-7.27 (m, 20H), 7.91 (d, 1H, $J = 9.0$ Hz), 8.15-8.26 (m, 2H), 8.52 (s, 1H), 8.76 (d, 1H, $J = 6.0$ Hz).

Preparation of Intermediate Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-Glutaminol).

A solution of cyclopentyl chlorothiolformate (0.133 g, 0.81 mmol), prepared as described in Example 37, in 2 mL of CH_2Cl_2 was added dropwise to a solution of L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol) hydrochloride salt (0.57 g, 0.81 mmol) in 10 mL of CH_2Cl_2 . To this solution was added 0.24 mL (1.7 mmol) of Et_3N . The reaction mixture was stirred for 15 min at rt, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel chromatography using a gradient solvent

system (0-2% MeOH/CHCl₃) to give 0.512 g (80%) of a white amorphous solid: IR (KBr) 3358, 2939, 1649, 1516, 1448, 1190, 700 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.13 (s, 3H), 1.23 (s, 3H), 1.37-1.63 (m, 10H), 1.96 (s, 3H), 1.98-2.01 (m, 1H), 2.16-2.33 (m, 1H), 2.7-2.89 (m, 1H), 3.07-3.23 (m, 2H), 3.24-3.28 (m, 1H), 3.53-3.57 (m, 1H), 3.59-3.66 (m, 1H), 4.37-4.47 (m, 1H), 4.54-4.60 (m, 2H), 7.14-7.28 (m, 20H), 7.55 (d, 1H, *J* = 9.0 Hz), 7.99 (d, 1H, *J* = 9.0 Hz), 8.36 (d, 1H, *J* = 6.0 Hz), 8.49 (s, 1H). MS calcd for C₄₅H₅₄N₄O₅S₂+H 795, found 795.

Preparation of Intermediates

Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-Glutaminal) &
Cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-(Tr-Glutaminal).

Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol) (0.46 g, 0.58 mmol) was dissolved in 10 mL of anhydrous DMSO. o-Iodoxybenzoic acid (0.48 g, 1.73 mmol) was added, and the reaction mixture was stirred at rt for 3 h. The DMSO was removed under high vacuum. The residue was twice diluted with CH₂Cl₂ and the solvent was evaporated to remove any residual DMSO. The residue was diluted with EtOAc, and triturated to form a white solid which was filtered off. The filtrate was washed with an aqueous 10% Na₂S₂O₃/10% NaHCO₃ solution, water and brine and dried over MgSO₄. Filtration and concentration gave 0.40 g (87%) of a white glassy solid which was used without further purification. The product was shown to be a mixture of the sulfide and sulfoxide by NMR analysis. ¹H NMR (DMSO-*d*₆) (mixture of sulfide and sulfoxide) δ 1.12 (s), 1.24 (s), 1.32 (s), 1.45-1.66 (m), 1.95-2.13 (m), 2.29 (s), 2.40 (s), 2.53 (s), 2.82-2.87 (m), 2.99-3.23 (m),

3.52-3.57 (m), 3.95-4.03 (m), 4.55-4.83 (m), 7.14-7.28 (m), 7.89-8.06 (m), 8.41-8.58 (m), 9.15 (s), 9.18 (s).

Preparation of Intermediates

Ethyl-3-[Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-Gln)]-E-Propenoate & Ethyl-3-(Cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-[Tr-Gln])-E-Propenoate.

The mixture of cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminal) and cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-(Tr-glutaminal) (0.40 g, approximately 0.51 mmol) was dissolved in 10 mL of anhyd THF. To this solution was added (carbethoxymethylene) triphenylphosphorane (0.21 g, 0.61 mmol), and the reaction mixture was stirred overnight at rt. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel using a gradient solvent system (0-2% MeOH/CHCl₃) to give 0.184 g of the sulfide product and 0.132 g sulfoxide product (contaminated with triphenylphosphine oxide):

Ethyl-3-[cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-Gln)]-E-propenoate: ¹H NMR (DMSO-*d*₆) δ 1.14 (s, 3H), 1.21 (t, 3H, *J* = 6.0 Hz), 1.24 (s, 3H), 1.46-1.68 (m, 10H), 1.96 (s, 3H), 2.25-2.31 (m, 2H), 2.78-2.85 (m, 1H), 2.96-3.00 (m, 1H), 3.54-3.72 (m, 1H), 4.05-4.13 (m, 2H), 4.32-4.47 (m, 1H), 4.49-4.55 (m, 1H), 4.56-4.59 (m, 1H), 5.57 (d, 1H, *J* = 15.0 Hz), 6.64 (dd, 1H, *J* = 15.0, 3.0 Hz), 7.13-7.26 (m, 20H), 7.99-8.04 (m, 2H), 8.45 (d, 1H, *J* = 9.0 Hz), 8.55 (s, 1H). Ethyl-3-(cyclopentylthiocarbonyl-

L-[S(O)-Me-Pen]-L-Phe-L-[Tr-Gln])-E-propenoate: ¹H NMR (DMSO-*d*₆) (mixture of diastereomers): δ 1.11-1.15 (m), 1.19-1.23 (m), 1.35-1.66 (m), 1.98-2.00 (m), 2.18-2.35 (m), 2.41 (s), 2.64-2.83 (m), 2.89-3.02 (m), 3.51-3.56 (m), 4.11 (q, *J* = 6.0 Hz), 4.34-4.40

(m), 4.48-4.59 (m), 4.63-4.66 (m), 5.51-5.57 (m), 6.61-6.68 (m), 7.13-7.28 (m), 8.12-8.24 (m), 8.42-8.53 (m), 8.55-8.57 (m).

Preparation of Product - Ethyl-3-[Cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-*Gln*]-E-Propenoate

Ethyl-3-[cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-*Gln*)]-E-propenoate (0.184 g) was dissolved in 10 mL CH_2Cl_2 . To this solution was added 1 mL of trifluoroacetic acid, and the reaction mixture was stirred at rt overnight. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using a gradient solvent system (0-2% $\text{MeOH}/\text{CHCl}_3$) to give 0.044 g (24%; 3 steps from cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol)) as a white amorphous solid: IR (KBr) 3296, 2984, 1787, 1655, 1560, 1541, 1280, 1194 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.14 (s, 3H), 1.21 (t, 3H, $J = 6.0$ Hz), 1.25 (s, 3H), 1.40-1.70 (m, 10H), 2.02 (s, 3H), 2.05-2.24 (m, 2H), 2.79-2.86 (m, 1H), 2.93-3.00 (m, 1H), 3.43-3.55 (m, 1H), 4.09 (q, 2H, $J = 6.0$ Hz), 4.31-4.36 (m, 1H), 4.43-4.50 (m, 1H), 4.56 (d, 1H, $J = 6.0$ Hz), 5.58 (d, 1H, $J = 15.0$ Hz), 6.65 (dd, 1H, $J = 15.0, 6.0$ Hz), 6.75 (bs, 1H), 7.15-7.21 (m, 6H), 7.99-8.06 (m, 2H), 8.45 (d, 1H, $J = 6.0$ Hz). HRMS calcd for $\text{C}_{30}\text{H}_{44}\text{N}_4\text{O}_6\text{S}_2 + \text{Cs}$ 753.1757, found 753.1737. Anal. ($\text{C}_{30}\text{H}_{44}\text{N}_4\text{O}_6\text{S}_2$) C, H, N, S.

Example 37 - Preparation of Compound 173: Ethyl-3-[Cyclopentylthiocarbonyl]-L-(S-Ph-Cys)-L-Phe-L-Gln]-E-Propenoate.

Preparation of Intermediate Cyclopentyl Chlorothiolformate.

Cyclopentanethiol (10.7 mL, 0.1 mol) was dissolved in 200 mL of CH_2Cl_2 . Triphosgene (11.13 g, 37.5 mmol) was added and the reaction mixture was cooled to 0 °C. Et_3N (14.1 mL, 0.1 mol) was added dropwise, and the reaction was allowed to warm to room temperature over a period of one hour. The solvent was carefully removed under reduced pressure at 20 °C due to the volatility of the product. The resulting residue was taken up in Et_2O , and the solids were filtered and washed with more Et_2O . The solvent was again carefully removed under reduced pressure, and the was product purified by distillation (85% yield): colorless liquid (bp 70-74 °C; 1 torr): IR(neat) 1756, 830 cm^{-1} ; ^1H NMR (benzene- d_6) δ 1.01-1.23 (m, 6H), 1.49-1.60 (m, 2H), 3.20-3.29 (m, 1H).

Preparation of Intermediate BOC-L-(S-Ph-Cys).

To a suspension of 19.73 g (0.1 mol) L-(S-Ph-Cys) (purchased from Davos Chemical Corp., Englewood Cliffs, NJ) in 72 mL of *tert*-butanol was added a solution of NaOH (4.1 g, 0.1025 mol) in 100 mL H_2O . Once the suspension became a clear solution di-*tert*-butyl dicarbonate (22.92 g, 0.105 mol) was added. The clear solution became a slurry and was allowed to stir at rt overnight. At this time the turbid solution was washed twice with pet. ether. The organic layer was washed 3 times with a sat NaHCO_3 solution and the aqueous layers were combined. The aqueous layer was then carefully acidified to pH 2-3 with a sat KHSO_4 solution and extracted with a large excess of Et_2O . The organic

phase was dried over Na_2SO_4 , filtered and concentrated under vacuum to give 27.4 g (92%) of BOC-L-(S-Ph-Cys) as white solid. Any residual H_2O and/or *tert*-butanol was removed by benzene azeotrope before using the material. ^1H NMR ($\text{DMSO}-d_6$) δ 1.36 (s, 9H), 3.10 (dd, 1H, $J = 13.6, 9.6$ Hz), 3.34 (dd, 1H, $J = 13.6, 4.4$ Hz), 4.01 (m, 1H), 7.20 (m, 2H), 7.34 (m, 3H), 12.82 (bs, 1H).

Preparation of Intermediate BOC-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol).

BOC-L-(S-Ph-Cys) (0.45 g, 1.5 mmol) was dissolved in 2 mL of DMF and 2 mL of CH_2Cl_2 . To this solution was added N-hydroxysuccinimide (0.17 g, 1.5 mmol), followed by dicyclohexylcarbodiimide (0.31 g, 1.5 mmol). The reaction was stirred at rt for 2 h. The mixture was then filtered into a separate flask containing L-Phe-L-(Tr-glutaminol) (0.78 g, 1.5 mmol) dissolved in 4 mL of DMF and 2 mL of CH_2Cl_2 . The reaction mixture was stirred overnight and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using a gradient solvent system (0-2% MeOH/ CHCl_3) to give 1.06 g (88%) of a white amorphous solid: IR (KBr) 3304, 3061, 2972, 2928, 1645, 1516, 1493, 1367, 1248, 1165, 1024, 742, 698 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.35 (s, 9H), 1.35-1.43 (m, 1H), 1.70-1.74 (m, 1H), 2.20-2.33 (m, 2H), 2.82-2.92 (m, 1H), 2.93-3.10 (m, 1H), 3.11-3.23 (m, 2H), 3.24-3.32 (m, 2H), 3.58-3.68 (m, 1H), 3.80-3.98 (m, 1H), 4.58-4.64 (m, 1H), 4.65-4.77 (m, 1H), 7.14-7.30 (m, 26H), 7.75 (d, 1H, $J = 6.0$ Hz), 7.83 (d, 1H, $J = 6.0$ Hz), 8.51 (s, 1H). MS calcd for $\text{C}_{47}\text{H}_{52}\text{N}_4\text{O}_6\text{S}+\text{H}$ 801, found 801.

Preparation of Intermediate L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) Hydrochloride Salt.

Using the procedure described in Example 36 for the preparation of L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol) hydrochloride salt, L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) hydrochloride salt was synthesized from BOC-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) to give 0.182 g of white solid which was used without further purification: IR (KBr) 3325, 3057, 2949, 1685, 1655, 1560, 1493, 1448, 746, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.41-1.67 (m, 1H), 1.69-1.81 (m, 1H), 2.26-2.44 (m, 2H), 2.86-2.97 (m, 1H), 2.98-3.23 (m, 1H), 3.25-3.43 (m, 4H), 3.60-3.84 (m, 2H), 4.02-4.20 (m, 1H), 4.44-4.60 (m, 1H), 7.08-7.48 (m, 25H), 7.87 (d, 1H, $J = 6.0$ Hz), 8.46 (bs, 3H), 8.55 (s, 1H), 8.87 (d, 1H, $J = 6.0$ Hz).

Preparation of Intermediate Cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 36 for the preparation of cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol), cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) was synthesized from L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) hydrochloride salt in 75% yield: white amorphous solid: IR (KBr) 3288, 3059, 2960, 1637, 1494, 1448, 1205, 746, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.42-1.98 (m, 10H), 1.99-2.26 (m, 1H), 2.48-2.50 (m, 1H), 2.96-2.98 (m, 1H), 3.01-3.19 (m, 1H), 3.19-3.55 (m, 6H), 3.64-3.85 (m, 1H), 4.36-4.40 (m, 1H), 4.46-4.58 (m, 1H), 7.14-7.30 (m, 25H), 7.68 (d, 1H, $J = 6.0$ Hz), 8.01 (d, 1H, $J = 6.0$ Hz), 8.41 (d, 1H, $J = 6.0$ Hz), 8.52 (s, 1H). MS calcd for $\text{C}_{48}\text{H}_{52}\text{N}_4\text{O}_5\text{S}_2 + \text{H}$ 829, found 829.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-Glutaminal).

Using the procedure described in Example 36 for the preparation of cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminal) and cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-(Tr-glutaminal), cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminal) was synthesized from cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminol) in 98% yield: white amorphous solid used without further purification: ¹H NMR (DMSO-*d*₆) δ 1.45-1.70 (m, 8H), 2.02-2.28 (m, 3H), 2.35-2.51 (m, 1H), 2.95-3.02 (m, 2H), 3.04-3.22 (m, 1H), 3.24-3.36 (m, 1H), 3.56-3.59 (m, 1H), 4.02-4.08 (m, 1H), 4.47-4.59 (m, 1H), 4.60-4.80 (m, 1H), 7.20-7.36 (m, 25H), 8.22 (d, 1H, *J* = 6.0 Hz), 8.43-8.48 (m, 2H), 8.65 (s, 1H), 9.27 (s, 1H).

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-*Met* (sulfoxide)]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-Gln)]-E-propenoate was synthesized from cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminal) to give 0.26 g of material contaminated with triphenylphosphine oxide (after column chromatography) which was used without further purification: ¹H NMR (DMSO-*d*₆) δ 1.19 (t, 3H, *J* = 6.0 Hz), 1.47-1.59 (m, 10H), 1.93-2.23 (m, 1H), 2.25-2.34 (m, 1H), 2.83-2.93 (m, 1H), 2.95-3.16 (m, 1H),

3.19-3.29 (m, 2H), 3.51-3.56 (m, 1H), 4.09 (q, 2H, $J = 6.0$ Hz), 4.35-4.44 (m, 2H), 4.46-4.48 (m, 1H), 5.64 (d, 1H, $J = 15.0$ Hz), 6.68 (dd, 1H, $J = 15.0, 3.0$ Hz), 7.13-7.29 (m, 25H), 8.07 (d, 1H, $J = 6.0$ Hz), 8.13 (d, 1H, $J = 6.0$ Hz), 8.42 (d, 1H, $J = 6.0$ Hz), 8.58 (s, 1H).

Preparation of Product - Ethyl-3-[Cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-Gln]-E-propenoate was synthesized from ethyl-3-[cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-Gln)]-E-propenoate in 35% yield (2 steps from cyclopentylthiocarbonyl-L-(S-Ph-Cys)-L-Phe-L-(Tr-glutaminal)): white amorphous solid: IR (KBr) 3294, 1712, 1655, 1633, 1545, 1203, 738, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.19 (t, 3H, $J = 6.0$ Hz), 1.56-1.76 (m, 10H), 1.98-2.08 (m, 2H), 2.84-2.99 (m, 2H), 3.17-3.39 (m, 2H), 3.51-3.76 (m, 1H), 4.08 (q, 2H, $J = 6.0$ Hz), 4.39-4.45 (m, 3H), 5.64 (d, 1H, $J = 15.0$ Hz), 6.69 (dd, 1H, $J = 15.0, 3.0$ Hz), 6.77 (bs, 1H), 7.18-7.32 (m, 11H), 8.08 (d, 1H, $J = 6.0$ Hz), 8.18 (d, 1H, $J = 6.0$ Hz), 8.43 (d, 1H, $J = 6.0$ Hz). HRMS calcd for $\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_6\text{S}_2 + \text{Cs}$ 787.1600, found 787.1618. Anal. ($\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_6\text{S}_2$) C, H, N, S.

Example 38 - Preparation of Compound 174: Ethyl-3-[Cyclopentylthiocarbonyl]-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-Propenoate.

Preparation of Intermediate Fmoc-L-(4-Me-Phe)-L-(Tr-Glutaminol).

Using the procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninol, this derivative was synthesized from Fmoc-L-4-Me-Phe (purchased from Neosystems Laboratories, Strasbourg, France) and L-(Tr-glutaminol) in 85% yield and isolated as a white solid. IR (KBr) 3316, 3283, 3024, 2946, 1694, 1667, 1448, 1256, 1041, 760, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.56 (m, 1H), 1.77 (m, 1H), 2.22 (s, 3H), 2.26 (m, 2H), 2.74 (m, 1H), 2.90 (m, 1H), 3.17 (m, 1H), 3.69 (m, 1H), 4.03-4.23 (m, 4H), 7.03-7.54 (m, 21H), 7.39 (t, 2H, $J = 7.4$ Hz), 7.50 (d, 1H, $J = 8.5$ Hz), 7.59 (d, 1H, $J = 7.4$ Hz), 7.60 (d, 1H, $J = 7.7$ Hz), 7.70 (d, 1H, $J = 8.8$ Hz), 7.87 (d, 2H, $J = 7.4$ Hz), 8.45 (s, 1H); MS calcd for $\text{C}_{49}\text{H}_{47}\text{N}_3\text{O}_5 + \text{Cs}$ 890, found 890.

Preparation of Intermediate L-(4-Me-Phe)-L-(Tr-Glutaminol).

To a solution of Fmoc-L-(4-Me-Phe)-L-(Tr-glutaminol) (3.25 g, 4.29 mmol) in anhydrous DMF (10 mL) was added piperidine (0.51 mL, 5.15 mmol). The solution was stirred and monitored by TLC. Upon consumption of the starting material, the reaction mixture was concentrated to a residue and then subjected to column chromatography on silica gel (5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford the product as white solid in 87% yield. IR (KBr) 3326, 3054, 3030, 2953, 2872, 1651, 1516, 1491, 1447, 1036, 700 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.47 (m, 1H), 1.75 (m, 3H), 2.13 (m, 1H), 2.23 (s, 3H), 2.57 (dd, 1H, $J = 13.2, 8.1$ Hz), 2.88 (dd, 1H, $J = 13.6, 4.8$ Hz), 3.20 (m, 1H), 3.30 (m, 1H), 3.66 (m, 1H), 4.64 (t, 1H, $J = 5.5$ Hz),

7.07 (m, 4H), 7.10-7.28 (m, 15H), 7.62 (d, 1H, $J = 8.8$ Hz), 8.54 (s, 1H); MS calcd for $C_{34}H_{37}N_3O_3 + Na$ 558, found 558.

Preparation of Intermediate Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly).

A stirred suspension of L- α -(t-butyl-Gly) (0.656 g, 5.0 mmol) in 18 mL CH_2Cl_2 , and diisopropylethylamine (3.5 mL, 20 mmol) was cooled to 0 °C. To this mixture chlorotrimethylsilane (0.83 mL, 6.5 mmol) was added dropwise. The slurry was allowed to warm to rt, and the mixture was stirred for about 2 h. At this time the mixture was recooled to 0 °C, and cyclopentyl chlorothiolformate (0.823 g, 5.0 mmol) was added dropwise. The slurry became a pale yellow solution after stirring at rt for approximately 5 h. The solution was concentrated, redissolved in an excess of EtOAc and washed with H_2O , 10% aq $KHSO_4$, H_2O and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give cyclopentylthiocarbonyl-L- α -(t-butyl-Gly) as a yellow oil in nearly quantitative yield which was azeotroped with benzene to remove any residual water before being used in the next step. IR (film) 3324, 2965, 2920, 2872, 1726, 1642, 1518, 1202 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.48-1.73 (m, 6H), 2.10 (m, 2H), 3.72 (m, 1H), 4.46 (m, 1H), 5.79 (m, 1H); MS calcd for $C_{12}H_{21}NO_3S + Na$ 282, found 282.

Preparation of Intermediate Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Glutaminol).

This preparation was carried out following the procedure of L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397. Cyclopentylthiocarbonyl-L- α -(t-butyl-Gly) (0.325 g, 1.25

mmol) was dissolved in 8.0 mL of DMF. Diisopropylethylamine (0.45 mL, 2.5 mmol) was added, followed by 0.67 g (1.25 mmol) of N-Me-L-(4-Me-Phe)-L-(Tr-glutaminol). The reaction was cooled to 0 °C and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.476 g, 1.25 mmol) was added. The reaction mixture was allowed to warm to rt whereupon the DMF was removed in vacuo. The residue was dissolved with EtOAc, and the organic phase washed consecutively with 1N HCl, a sat NaHCO₃ solution, H₂O, and brine. The solvent was dried over MgSO₄, filtered, and concentrated to give a residue which was subjected to column chromatography on silica gel (gradient; 2-5% MeOH/CHCl₃) to give 0.95 g (98%) of a white amorphous solid: IR(KBr) 3302, 2957, 2876, 1669, 1645, 1537, 1447, 1196, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (s, 9H), 1.48-1.70 (m, 9H), 1.85 (m, 1H), 2.04 (m, 2H), 2.28 (s, 3H), 2.32 (m, 2H), 2.92 (m, 2H), 3.25 (dd, 1H, *J* = 8.1, 3.5 Hz), 3.30 (dd, 1H, *J* = 10.9, 3.7 Hz), 3.66 (m, 1H), 3.72 (m, 1H), 4.14 (m, 1H), 4.47 (m, 1H), 6.04 (d, 1H, *J* = 7.7 Hz), 6.52 (d, 1H, *J* = 7.7 Hz), 6.60 (d, 1H, *J* = 7.0 Hz), 7.05 (m, 5H), 7.24 (m, 15H). MS calcd for C₄₆H₅₆N₄O₅S+Na 799, found 799.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Glutaminal).

Using the general procedure described in Example 1 for the preparation of CBZ-L-Leu-L-Phe-L-methioninal (sulfoxide), cyclopentylthiocarbonyl-L-α-(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminal) was synthesized from cyclopentylthiocarbonyl-L-α-(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminol) in quantitative yield and isolated as a

white amorphous solid and used without further purification: IR(film) 3302, 3061, 3030, 2961, 2870, 1730, 1644, 1514, 1493, 1196, 911, 733, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.90 (s, 9H), 1.46-1.68 (m, 8H), 1.86 (m, 1H), 2.00-2.24 (m, 2H), 2.28 (s, 3H), 2.31 (m, 1H), 2.96 (m, 2H), 3.58 (m, 1H), 4.05 (m, 1H), 4.14 (m, 1H), 4.52 (m, 1H), 5.88 (m, 1H), 6.28 (m, 1H), 6.90 (m, 1H), 7.07 (m, 5H), 7.25 (m, 15H), 9.30 (s, 1H); MS calcd for $\text{C}_{46}\text{H}_{54}\text{N}_4\text{O}_5\text{S}\cdot\text{CH}_3\text{OH}$ (methyl-hemiacetal)+Na 829, found 829.

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-*Met* (sulfoxide)]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-propenoate was synthesized from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminal) (0.468 g, 0.627 mmol) to give 0.52 g of material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient: 1-2.5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$), which was used without further purification: white amorphous solid: IR(film) 3302, 3061, 2967, 2868, 1721, 1642, 1514, 1491, 1370, 1192, 1036, 911, 731, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.72 (s, 9H), 1.29 (t, 3H, $J = 7.0$ Hz), 1.46-1.68 (m, 6H), 1.86-2.05 (m, 4H), 2.29 (s, 3H), 2.32 (m, 2H), 2.91 (m, 2H), 3.00 (m, 1H), 3.62 (m, 1H), 4.07 (m, 1H), 4.17 (q, 2H, $J = 7.2$ Hz), 4.43 (m, 2H), 5.61 (dd, 1H, $J = 15.8, 1.5$ Hz), 5.95 (m, 1H), 6.34 (m, 1H), 6.57 (m, 1H), 6.64 (dd, 1H, $J = 15.8, 5.5$ Hz), 7.03 (m, 5H), 7.24 (m, 15H). MS calcd for $\text{C}_{50}\text{H}_{60}\text{N}_4\text{O}_6\text{S}+\text{Na}$ 867, found 867.

Preparation of Product - Ethyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-propenoate was synthesized from ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-propenoate and isolated as a white solid after purification by column chromatography on silica gel using a gradient solvent system (1-5% MeOH/CH₂Cl₂) (57% yield; two steps from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminal): IR (KBr) 3318, 2973, 2951, 2868, 1715, 1651, 1539, 1371, 1192 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.83 (s, 9H), 1.21 (t, 3H, *J* = 7.2 Hz), 1.41-1.72 (m, 8H), 2.02 (m, 4H), 2.22 (s, 3H), 2.81 (m, 2H), 3.54 (m, 1H), 4.10 (q, 2H, *J* = 7.0 Hz), 4.24 (d, 1H, *J* = 9.3 Hz), 4.36 (m, 1H), 4.43 (m, 1H), 5.56 (dd, 1H, *J* = 15.7, 1.4 Hz), 6.65 (dd, 1H, *J* = 15.7, 5.5 Hz), 6.73 (s, 1H), 7.03 (m, 4H), 7.13 (s, 1H), 7.86 (d, 1H, *J* = 9.3 Hz), 8.04 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 7.8 Hz); HRMS calcd for C₃₁H₄₆N₄O₆S+Cs 735.2192, found 735.2180. Anal. (C₃₁H₄₆N₄O₆S) C, H, N, S.

Example 39 - Preparation of Compound 175: Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-Propenoate.

Preparation of Intermediate Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-Met (sulfoxide)]-E-propenoate, ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-propenoate was synthesized from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminal) (0.466 g, 0.60 mmol) and (carbethoxyethylidene)triphenylphosphorane (0.24 g, 0.66 mmol) to give 0.487 g of material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient: 1-2.5% MeOH/CH₂Cl₂) which was used without further purification. white amorphous solid: IR(film) 3302, 3063, 2967, 2870, 1711, 1642, 1516, 1491, 1250, 1194, 911, 731, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (s, 9H), 1.31 (t, 3H, *J* = 7.2 Hz), 1.50-1.77 (m, 6H), 1.81 (m, 2H), 1.82 (s, 3H), 2.06 (m, 2H), 2.28 (s, 3H), 2.31 (m, 2H), 2.93 (m, 2H), 3.64 (m, 1H), 4.04 (m, 1H), 4.20 (q, 2H, *J* = 7.0 Hz), 4.40 (m, 1H), 4.58 (m, 1H), 5.90 (m, 1H), 6.30 (m, 3H), 7.01 (m, 5H), 7.24 (m, 15H). MS calcd for C₅₁H₆₂N₄O₆S+Na 881, found 881.

Preparation of Product - Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-Gln]-E-propenoate was synthesized from ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-Gln)]-E-propenoate and isolated as a white solid after purification by column chromatography on silica gel using a gradient solvent system (1-5% MeOH/CH₂Cl₂) (55% yield; two steps from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminal): IR (KBr) 3324, 2963, 2870, 1707, 1647, 1550, 1516, 1257, 1196 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.83 (s, 9H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.41-1.73 (m, 8H), 1.77 (m, 3H), 2.00 (m, 4H), 2.20 (s, 3H), 2.78 (m, 2H), 3.55 (m, 1H), 4.12 (q, 2H, *J* = 7.0 Hz), 4.23 (d, 1H, *J* = 9.0 Hz), 4.35 (m, 1H), 4.48 (m, 1H), 6.29 (dd, 1H, *J* = 9.3, 1.2 Hz), 6.72 (s, 1H), 6.99 (m, 4H), 7.13 (s, 1H), 7.86 (d, 1H, *J* = 9.0 Hz), 8.03 (m, 2H); HRMS calcd for C₃₂H₄₈N₄O₆S+Cs 749.2349, found 749.2336. Anal. (C₃₂H₄₈N₄O₆S) C, H, N, S.

Example 40 - Preparation of Compound 176: Ethyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-Propenoate.**Preparation of Intermediate Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-Glutaminol).**

This intermediate was prepared as a white solid in 75% yield from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly) and the free base of

L-(4-F-Phe)-L-(Tr-glutaminol)·HCl using the procedure described to prepare cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-Me-Phe)-L-(Tr-glutaminol). IR(KBr) 3299, 3063, 2969, 2870, 1651, 1510, 1447, 1225, 1192, 766, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.88 (s, 9H), 1.50-1.76 (m, 9H), 1.85 (m, 1H), 2.05 (m, 2H), 2.36 (m, 2H), 2.50 (m, 1H), 2.92 (m, 2H), 3.32 (m, 2H), 3.66 (m, 1H), 3.73 (m, 1H), 4.17 (m, 1H), 4.69 (m, 1H), 6.09 (d, 1H, $J = 7.0$ Hz), 6.74 (m, 1H), 6.91 (m, 2H), 7.05 (m, 2H), 7.24 (m, 15H). MS calcd for $\text{C}_{46}\text{H}_{53}\text{N}_4\text{O}_5\text{SF}+\text{Na}$ 803, found 803.

Preparation of Intermediate Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-Glutaminal).

Using the general procedure described in Example 1 for the preparation CBZ-L-Leu-L-Phe-L-methioninal (sulfoxide), cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-glutaminal) was synthesized from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-glutaminol) in quantitative yield and isolated as a white amorphous solid and used without further purification: IR(film) 3302, 3061, 3030, 2961, 2866, 1732, 1644, 1510, 1447, 1225, 1196, 911, 733, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.90 (s, 9H), 1.48-1.67 (m, 8H), 1.85 (m, 1H), 2.00-2.28 (m, 2H), 2.36 (m, 2H), 2.90 (dd, 1H, $J = 14.9, 6.1$ Hz), 3.03 (dd, 1H, $J = 14.5, 6.8$ Hz), 3.64 (m, 1H), 4.07 (m, 1H), 4.18 (m, 1H), 4.53 (m, 1H), 5.92 (m, 1H), 6.31 (m, 1H), 6.92 (m, 2H), 7.10 (m, 3H), 7.23 (m, 15H), 9.31 (s, 1H); MS calcd for $\text{C}_{45}\text{H}_{53}\text{N}_4\text{O}_5\text{SF}\cdot\text{CH}_3\text{OH}$ (methyl-hemiacetal)+Na 833, found 833.

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-Met (sulfoxide)]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-Gln)]-E-propenoate was synthesized from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-glutaminal) (0.343 g, 0.44 mmol) to give 0.377 g of material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient: 1-2.5% MeOH/CH₂Cl₂) which was used without further purification: white amorphous solid: IR(KBr) 3314, 3285, 2969, 2936, 1723, 1651, 1510, 1447, 1370, 1190, 1038, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (s, 9H), 1.28 (t, 3H, J = 7.0 Hz), 1.48-1.78 (m, 8H), 1.83-2.15 (m, 4H), 2.32 (m, 2H), 2.85 (m, 1H), 3.00 (m, 1H), 3.61 (m, 1H), 4.16 (q, 2H, J = 7.0 Hz), 4.39 (m, 2H), 5.54 (d, 1H, J = 15.4 Hz), 6.17 (m, 1H), 6.63 (dd, 1H, J = 15.4, 4.0 Hz), 6.91 (m, 2H), 7.01 (m, 2H), 7.28 (m, 15H), 7.45 (m, 1H), 7.54 (m, 1H), 7.63 (m, 1H). MS calcd for C₄₉H₅₇N₄O₆SF+Na 871, found 871.

Preparation of Product - Ethyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L- α -(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-propenoate was synthesized from ethyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-

L-(Tr-Gln)]-E-propenoate and isolated as a white solid after purification by column chromatography on silica gel using a gradient solvent system (1-5% MeOH/CH₂Cl₂) (56% yield; two steps from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-

L-(Tr-glutaminal): IR (KBr) 3310, 2961, 2868, 1713, 1649, 1512, 1192 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.83 (s, 9H), 1.21 (t, 3H, *J* = 7.2 Hz), 1.40-1.69 (m, 8H), 2.01 (m, 4H), 2.80 (dd, 1H, *J* = 14.0, 8.1 Hz), 2.90 (dd, 1H, *J* = 13.2, 7.0 Hz), 3.54 (quin, 1H, *J* = 7.2 Hz), 4.09 (q, 2H, *J* = 6.9 Hz), 4.28 (d, 1H, *J* = 9.6 Hz), 4.38 (m, 1H), 4.47 (m, 1H), 5.48 (dd, 1H, *J* = 15.6, 1.3 Hz), 6.64 (dd, 1H, *J* = 15.6, 5.3 Hz), 6.74 (bs, 1H), 7.00 (t, 2H, *J* = 8.8 Hz), 7.13 (bs, 1H), 7.20 (d, 1H, *J* = 8.5 Hz), 7.22 (d, 1H, *J* = 8.5 Hz), 7.88 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 7.7 Hz); HRMS calcd for C₃₀H₄₃N₄O₆SF+Cs 739.1942, found 739.1954. Anal. (C₃₀H₄₃N₄O₆SF) C, H, N, S.

Example 41 - Preparation of Compound 177: Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-Propenoate.

Preparation of Intermediate Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L- α -(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-Gln)]-E-Propenoate.

Using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-Leu-L-Phe-L-Met (sulfoxide)]-E-propenoate, ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-Gln)]-E-propenoate was synthesized from cyclopentylthiocarbonyl-L- α -(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-glutaminal) (0.297 g, 0.38 mmol) and (carbethoxyethylidene)triphenylphosphorane (0.152 g, 0.42 mmol) to give 0.377 g of

material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient: 1-2.5% MeOH/CH₂Cl₂) which was used without further purification. white amorphous solid: IR(film) 3356, 3291, 3063, 2973, 2951, 1711, 1651, 1510, 1447, 1256, 1190, 752, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (s, 9H), 1.31 (t, 3H, *J* = 7.0 Hz), 1.51-1.83 (m, 11H), 2.17 (m, 2H), 2.28 (m, 2H), 2.75-3.02 (m, 2H), 3.66 (m, 1H), 4.16 (m, 3H), 4.45 (m, 1H), 4.60 (m, 1H), 6.30 (m, 2H), 6.58 (m, 1H), 6.78 (m, 1H), 6.88 (m, 2H), 6.98 (m, 3H), 7.20 (m, 15H). MS calcd for C₃₀H₃₉N₄O₆SF+Na 885, found 885.

Preparation of Product - Ethyl-2-Methyl-3-[Cyclopentylthiocarbonyl-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-Propenoate.

Using the procedure described in Example 34 for the preparation of ethyl-3-[ethylthiocarbonyl-L-α-(t-butyl-Gly)-L-Phe-L-Gln]-E-propenoate, ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L-α-(t-butyl-Gly)-L-(4-F-Phe)-L-Gln]-E-propenoate was synthesized from ethyl-2-methyl-3-[cyclopentylthiocarbonyl-L-α-(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-Gln)]-E-propenoate and isolated as a white solid after purification by column chromatography on silica gel using a gradient solvent system (1-5% MeOH/CH₂Cl₂) (55% yield; two steps from cyclopentylthiocarbonyl-L-α-(t-butyl-Gly)-L-(4-F-Phe)-L-(Tr-glutaminal): IR (KBr) 3326, 2951, 2868, 1713, 1645, 1553, 1510, 1260, 1194 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.83 (s, 9H), 1.22 (t, 3H, *J* = 7.0 Hz), 1.41-1.75 (m, 8H), 1.77 (m, 3H), 1.92 (m, 4H), 2.77 (dd, 1H, *J* = 13.8, 8.3 Hz), 2.85 ((dd, 1H, *J* = 13.6, 7.0 Hz), 3.55 (quin, 1H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 4.22 (d, 1H, *J* = 9.2 Hz), 4.38 (m, 1H), 4.45 (m, 1H), 6.24 (dd, 1H, *J* = 9.2, 1.5

Hz), 6.72 (bs, 1H), 6.96 (t, 2H, $J = 8.8$ Hz), 7.87 (d, 1H, $J = 8.8$ Hz), 8.03 (d, 1H, $J = 8.1$ Hz), 8.11 (d, 1H, $J = 7.7$ Hz); HRMS calcd for $C_{31}H_{45}N_4O_6SF + Cs$ 753.2098, found 753.2084. Anal. ($C_{31}H_{45}N_4O_6SF$) C, H, N, S.

Example 42 - Preparation of Compound 179: Ethyl-3-(Cyclopentylthiocarbonyl)-L-[S(O)-Me-Pen]-L-Phe-L-Gln)-E-Propenoate.

Preparation of Product Ethyl-3-(Cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-Gln)-E-Propenoate

Using the procedure described in Example 36 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-Gln]-E-propenoate, ethyl-3-(cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-Gln)-E-propenoate was synthesized from ethyl-3-(cyclopentylthiocarbonyl-L-[S(O)-Me-Pen]-L-Phe-L-[Tr-Gln])-E-propenoate in 40% yield (3 steps from cyclopentylthiocarbonyl-L-(S-Me-Pen)-L-Phe-L-(Tr-glutaminol)): white amorphous solid: IR (KBr) 3302, 1662, 1541, 1458, 1205, 1138, 1028 cm^{-1} ; 1H NMR (DMSO- d_6) (mixture of diastereomers) δ 1.03 (s), 1.12 (s), 1.21 (t, 3H, $J = 6.0$ Hz), 1.42-1.76 (m), 2.0-2.21 (m), 2.34 (s), 2.42 (s), 2.80-2.87 (m), 2.93-3.11 (m), 3.47-3.60 (m), 4.10 (q, $J = 6.0$ Hz), 4.35-4.40 (m), 4.44-4.52 (m), 4.64 (d, $J = 6.0$ Hz), 5.58-5.62 (m), 6.60-6.70 (m), 6.75 (bs), 7.14-7.21 (m), 8.16-8.22 (m), 8.41 (d, $J = 9.0$ Hz), 8.54 (d, $J = 9.0$ Hz). HRMS calcd for $C_{30}H_{44}N_4O_7S_2 + Cs$ 769.1706, found 769.1727.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and

modifications can be made therein without departing from the spirit and scope thereof.

Thus, it is intended that the present invention cover the modifications and variations, provided they come within the scope of the appended claims and their equivalents.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Inhibition of Rhinovirus Protease

Stock solutions (50 mM, in DMSO) of various compounds were prepared; dilutions were in the same solvent. Recombinant Rhinovirus 3C proteases from serotypes 14, 16, 2 or 89 were prepared by the following standard chromatographic procedures: (1) ion exchange using Q Sepharose Fast Flow from Pharmacia; (2) affinity chromatography using Affi-Gel Blue from Biorad; and (3) sizing using Sephadex G-100 from Pharmacia. Assays contained 2% DMSO, 50 mM Tris pH 7.6, 1 mM EDTA, a compound at the indicated concentrations, approximately 1 μ M substrate, and 50-100 nM protease. For K_i determinations, the compound and the enzyme were preincubated for 10 minutes at 30 °C prior to addition of the substrate (substrate start). The k_{obs}/I values were obtained from reactions initiated by addition of enzyme rather than substrate. RVP activity is measured in the fluorescence resonance energy transfer assay. The substrate was (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Phe-Gln-Gly-Pro-Val-Gly)-EDANS. In the uncleaved peptide, the EDANS fluorescence was quenched by the proximal DABCYL moiety. When the peptide was cleaved, the quenching was relieved, and activity was measured as an increase in fluorescence signal. Data was analyzed using standard non linear fitting programs (Enzfit), and are shown Table 1.

TABLE 1

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs} (M-1sec-1)</u> |
|-------------------|------------|-------------------------|-----------------------------------|
| 1 | | 77 (50) | ND |
| 2 | | 6.6μM(K _i) | ND |
| 3 | | 81(0.1) | 37,000 |
| | (16) | | 6,500 |
| | (89) | | 3,400 |
| | (2) | | 1,900 |
| 4 | | 49(0.5) | 790 |
| 5 | | 7.1μM(K _i) | 221 |
| 6 | | 32μM(K _i) | 350 |
| 7 | | 9.5μM(K _i) | 2,400 |
| | (16) | 42(1) | ND |
| 8 | | 36μM(K _i) | 61 |
| 9 | | 20(1) | 160 |
| 10 | | 55(5) | 270 |
| 11 | | 28μM(K _i) | 20,000 |
| 12 | | 4.3μM(K _i) | 2,200 |
| 13 | | 6.5μM(K _i) | 54,000 |
| | (16) | | 9,000 |
| | (2) | | 2,400 |
| | (89) | | 5,500 |
| 14 | | NI | ND |
| 15 | | 55(50) | 27 |
| 16 | | 40(0.25) | 3,500 |
| 17 | | 1.25μM(K _i) | 6,100 |
| 18 | | 15.3μM(K _i) | 7,700 |
| 19 | | 35μM(K _i) | 7,900 |
| 20 | | NI | ND |
| 21 | | 9.9μM(K _i) | 2,100 |
| 22 | | 4.3μM(K _i) | 1,300 |
| 23 | | 177μM(K _i) | 120 |
| 24 | | ND | 500,000 |
| 25 | | 5.5μM(K _i) | 3,700 |
| 26 | | 52(0.1) | 5,400 |
| 27 | | 20μM(K _i) | 3,000 |
| 28 | | 57μM(K _i) | 4,000 |
| 29 | | ND | ND |
| 30 | | 373μM(K _i) | 430 |
| 31 | | 25(10) | 21 |

TABLE 1 (cont)

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/1 (M-1sec-1)</u> |
|-------------------|------------|-------------------------|-------------------------------------|
| 32 | | ND | 280 |
| 33 | | 24(10) | 33 |
| 34 | | 10(10) | 34 |
| 35 | | 16.5μM(K _i) | 46,388 |
| | (2) | ND | 2,357 |
| | (16) | ND | 9,177 |
| 36 | | 15μM(K _i) | 12,000 |
| 37 | | 18.8μM(K _i) | 5,900 |
| 38 | | >50μM(K _i) | 400 |
| 39 | | ND | 1,200 |
| 40 | | ND | 250 |
| 41 | | ND | 8,464 |
| 42 | | ND | 150,000 |
| 43 | | ND | 4,500 |
| 44 | | 12.6μM(K _i) | 21,000 |
| 45 | | NI | ND |
| 46 | | ND | 120,000 |
| 49 | | ND | 460,000 |
| 51 | | ND | 310,000 |
| 52 | | ND | 15,000 |
| 53 | | ND | 11,320 |
| 56 | | 15μM(K _i) | 5,624 |
| 59 | | 2.0μM(K _i) | 200 |
| 60 | | 5.0μM(K _i) | 575 |
| 61 | | ND | 125,940 |
| | (2) | ND | 14,000 |
| | (16) | ND | 25,000 |
| 62 | | ND | 600,000 |
| | (2) | ND | 600,000 |
| | (16) | ND | 300,000 |
| 65 | | 2.9μM(K _i) | ND |
| 66 | | ND | 400,000 |
| 67 | | ND | 9,600 |
| 68 | | 15μM(K _i) | 750 |
| 70 | | ND | 39,000 |
| 71 | | ND | 20,650 |

TABLE 1 (cont)

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/M-1sec-1</u> |
|-------------------|------------|------------------------|---------------------------------|
| 73 | | ND | 20,000 |
| | (2) | ND | 1,750 |
| | (16) | ND | 4,500 |
| 74 | | 2.4μM(K _i) | |
| 75 | | ND | |
| 76 | | 30μM(K _i) | ND |
| 77 | | 4.8μM(K _i) | ND |
| 78 | | 7.0μM(K _i) | |
| 79 | | ND | 13,900 |
| 80 | | ND | 200,000 |
| 81 | | ND | 124,000 |
| 82 | | 26μM(K _i) | 7,300 |
| 83 | | 8.0μM(K _i) | ND |
| 84 | | ND | 18,650 |
| 85 | | 3.0μM(K _i) | 6,500 |
| 86 | | 4.0μM(K _i) | 12,000 |
| 87 | | 6.0μM(K _i) | 5,430 |
| 88 | | >30μM(K _i) | 8,960 |
| 89 | | 5μM(K _i) | 53,360 |
| | (16) | ND | 2,800 |
| 90 | | ND | 10,918 |
| | (16) | ND | 3,600 |
| 91 | | 10μM(K _i) | 5,427 |
| 92 | | ND | 445 |
| 93 | | 30μM(K _i) | 3,444 |
| 94 | | 1.5μM(K _i) | 5,800 |
| 95 | | ND | <1000 |
| 96 | | ND | 300 |
| 97 | | ND | 12,900 |
| 98 | | ND | 91 |
| 99 | | 10 (50) | ND |
| 100 | | ND | 1,200 |
| 101 | | ND | 11,288 |
| 102 | | 12μM(K _i) | 3,845 |
| 103 | | ND | 29,200 |
| | (2) | ND | 1,106 |
| | (16) | ND | 3,354 |

TABLE 1 (cont)

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/I (M⁻¹sec⁻¹)</u> |
|-------------------|------------|--------------------------|---|
| 104 | | 2.5μM(K _i) | 8,000 |
| | (16) | 1.5μM(K _i) | ND |
| 105 | | ND | 1,200 |
| 106 | | 2.0μM(K _i) | 280,000 |
| | (2) | ND | 28,400 |
| | (16) | ND | 75,000 |
| 107 | | 13.5μM(K _i) | 3,655 |
| 108 | | ND | 4,694 |
| 109 | | ND | 1,348 |
| 110 | | ND | 9,072 |
| 111 | | 5.0μM(K _i) | 2,065 |
| 112 | | 13μM(K _i) | 6,800 |
| 113 | | ND | 8,877 |
| 114 | | ≥1.0μM(K _i) | 82,320 |
| | (2) | ND | 1,971 |
| 115 | | 11μM(K _i) | 4,485 |
| 116 | | ND | 23,670 |
| 117 | | ND | 18,760 |
| 118 | | 39μM(K _i) | 1,448 |
| 119 | | 5.0μM(K _i) | 69,800 |
| 120 | | 6.0μM(K _i) | 91,300 |
| | (2) | ND | 8,900 |
| | (16) | ND | 20,034 |
| 121 | | 12μM(K _i) | 238 |
| 122 | | ND | 1,252 |
| 123 | | ND | 890 |
| 124 | | ND | 1,000 |
| 125 | | ND | >500,000 |
| 126 | | ND | 29,000 |
| 127 | | ND | 28,347 |
| 128 | | ND | 22,691 |
| 129 | | ND | 230,000 |
| 130 | | 30-40nM(K _i) | ND |
| 131 | | NI | NI |
| 132 | | 10μM(K _i) | 10,800 |
| 133 | | ND | 9,600 |
| 134 | | ND | 1,769 |

TABLE 1 (cont)

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/1 (M-1sec-1)</u> |
|-------------------|------------|--------------------------------|-------------------------------------|
| 135 | | ND | 16,270 |
| | (2) | ND | 671 |
| | (16) | ND | 3,465 |
| 136 | | ND | 4,210 |
| 137 | | ND | 2,344 |
| | (2) | ND | 643 |
| | (16) | ND | 1,157 |
| 138 | | 20 μ M(K _i) | 1,769 |
| 139 | | ND | 43,140 |
| | (2) | ND | 691 |
| | (16) | ND | 1,259 |
| 140 | | ND | 7,122 |
| 141 | | ND | 2,309 |
| 142 | | ND | 2,929 |
| 143 | | ND | 2,963 |
| 144 | | ND | ND |
| 145 | | 10-20 μ M(K _i) | ND |
| 146 | | ND | 62,500 |
| | (2) | ND | 7,790 |
| | (16) | ND | 16,900 |
| 147 | | ND | 18,600 |
| | (2) | ND | 1,000 |
| | (16) | ND | 4,290 |
| 148 | | 1.0 μ M(K _i) | 57,000 |
| | (2) | ND | 8,300 |
| | (16) | ND | 14,800 |
| 149 | | ND | 39,940 |
| | (2) | ND | 2,840 |
| | (16) | ND | 7,700 |
| 150 | | ND | 573 |
| 151 | | >4.8 μ M(K _i) | 39,750 |
| 152 | | 3.2 μ M(K _i) | 38,900 |
| 153 | | 1.4 μ M(K _i) | 141,200 |
| | (2) | ND | 13,350 |
| | (16) | ND | 30,650 |
| 154 | | 1.1 μ M(K _i) | 78,900 |
| | (2) | ND | 5,400 |
| | (16) | ND | 13,900 |

TABLE 1

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/l (M⁻¹sec⁻¹)</u> |
|-------------------|------------|------------------------|---|
| 155 | | 4.2mM(K _i) | 59,425 |
| | (2) | ND | 1,390 |
| | (16) | ND | 5,250 |
| 156 | | ND | NI |
| 157 | | 6.0μM(K _i) | 161,500 |
| | (2) | ND | 9,700 |
| | (16) | ND | 30,800 |
| 158 | | 17μM(K _i) | 22,600 |
| | (2) | ND | 2,200 |
| | (16) | ND | 6,400 |
| 159 | | 0.5μM(K _i) | 35,000 |
| | (2) | ND | 2,500 |
| | (16) | ND | 6,500 |
| 160 | | ND | 312,000 |
| | (2) | ND | 26,710 |
| | (16) | ND | 50,000 |
| 161 | | ND | 1,086,000 |
| | (2) | ND | 200,000 |
| | (16) | ND | 126,000 |
| 162 | | ND | 800,000 |
| | (2) | ND | 150,000 |
| | (16) | ND | 80,000 |
| 163 | | 3.6μM(K _i) | 9,800 |
| 164 | | ND | 155,500 |
| 165 | | ND | 97,000 |
| | (2) | ND | 5,600 |
| | (16) | ND | 20,200 |
| 166 | | ND | 40,900 |
| | (2) | ND | 3,500 |
| | (16) | ND | 7,700 |
| 167 | | ND | 165,400 |
| | (2) | ND | 10,700 |
| | (16) | ND | 42,100 |
| 168 | | ND | 37,800 |
| 169 | | ND | 800 |
| 170 | | ND | 85,300 |
| | (2) | ND | 8,400 |
| | (16) | ND | 30,000 |

TABLE 1

| <u>COMPOUND #</u> | <u>RVP</u> | <u>INHIB</u> | <u>k_{obs}/I (M⁻¹sec⁻¹)</u> |
|-------------------|------------|-------------------------------|---|
| 171 | | ND | 21,200 |
| | (2) | ND | 830 |
| | (16) | ND | 3,250 |
| 172 | | ND | 31,700 |
| | (2) | ND | 2,000 |
| | (16) | ND | 6,000 |
| 173 | | ND | 1,000,000 |
| | (2) | ND | 113,000 |
| | (16) | ND | 185,000 |
| 174 | | ND | 800,000 |
| 175 | | ND | 124,000 |
| 176 | | 0.48 μ M(K _i) | 240,000 |
| 177 | | ND | 80,300 |
| 178 | | ND | 286,300 |
| 179 | | 0.36 μ M(K _i) | 300,000 |
| 180 | | 0.42 μ M(K _i) | 300,000 |
| 181 | | ND | 1,000,000 |
| 182 | | ND | 114,360 |
| 183 | | 0.55 μ M(K _i) | 500,000 |
| | (16) | ND | 60,000 |
| 184 | | ND | 59,900 |
| 185 | | ND | 600,000 |
| 186 | | ND | 950,000 |
| 187 | | NI | ND |
| 188 | | 0.16 μ M(K _i) | 580,000 |
| 189 | | ND | 386,000 |
| 190 | | ND | 29,230 |

In the above table, all data is for RVP serotype-14 unless otherwise noted in parentheses. All strains of human rhinovirus (HRV) were purchased from American Type Culture Collection (ATCC), except for serotype 14, which was produced from the infectious cDNA clone constructed and supplied to us by Dr. Roland Rueckert at the Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. The

column designated INHIB represents the percent inhibition, with the concentration of the compound in μM indicated in parentheses, unless K_i was assigned as designated by (K_i), at 10 minute preincubation with 50 nM RVP prior to addition of substrate was used. The data in the column designated k_{obs} was measured from progress curves in enzyme start experiments. The designation NI indicates that no inhibition was obtained when 10 μM of a compound was used. The designation ND indicates that a value was not determined for that compound.

Antirhinoviral HI-HeLa Cell Culture Assay

In the Cell Protection Assay, the ability of compounds to protect cells against HRV infection was measured by the XTT dye reduction method. This method is described in Weislow, O.S., R. Kiser, D.L. Fine, J. Bader, R.H. Shoemaker, and M.R. Boyd, *J. Natl. Cancer Inst.* 1989, 81, 577-586, which is incorporated herein by reference.

HI-HeLa cells were infected with HRV-14 at a multiplicity of infection (m.o.i.) of 0.13 (virus particles/cell) or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8×10^5 cells per mL and incubated with appropriate concentrations of compounds of formulas I and II. Two days later, XTT/PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free mock-infected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan

produced in compound-treated, mock-infected cells to 50% of that produced in compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50} .

All strains of human rhinovirus (HRV) for use in this assay were purchased from American Type Culture Collection (ATCC), except for HRV serotype-14, which was produced from the infectious cDNA clone, constructed and supplied to us by Dr. Roland Rueckert at the Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. HRV stocks were propagated, and antiviral assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium, available from Life Technologies, with 10% fetal bovine serum.

The compounds were tested against control compounds WIN 51711, WIN 52084, and WIN 54954, all obtained from Sterling-Winthrop Pharmaceuticals, and control compound Pirodavir, obtained from Janssen Pharmaceuticals.

TABLE 2

| Compound # | EC_{50} (μ M) | CC_{50} (μ M) | TI |
|------------|----------------------|----------------------|------|
| 1 | ND | ND | |
| 2 | 100 | >320 | >3.2 |
| 3 | 0.61 | >320 | >525 |
| 4 | 2.2 | >320 | >146 |
| 5 | 1.6 | 251 | 157 |
| 6 | >320 | >320 | |

| | | | |
|----|------|------|------|
| 7 | 3.2 | >320 | >100 |
| 8 | >320 | >320 | >5 |
| 9 | >320 | >320 | |
| 10 | 200 | >320 | >2 |
| 11 | 1.3 | >320 | >246 |
| 12 | 1.6 | >100 | >63 |
| 13 | 2.0 | 58.9 | 29 |
| 14 | 17.8 | 500 | 28 |
| 15 | >100 | >100 | |
| 16 | 32 | >100 | >3 |
| 17 | 1.8 | >100 | >56 |
| 18 | 0.64 | >100 | >156 |
| 19 | 1.35 | >100 | >74 |
| 20 | >320 | >320 | |
| 21 | 22.4 | >100 | >5 |
| 22 | 56.2 | 251 | >5 |
| 23 | >100 | >100 | |
| 24 | 4.0 | 16 | 4 |
| 25 | 3.1 | >100 | >33 |
| 26 | 2.0 | 44.7 | 22 |
| 27 | 3.5 | 160 | 46 |
| 28 | 4.5 | 63.1 | 14 |
| 29 | 27 | 500 | 19 |
| 30 | 5.6 | 100 | 18 |
| 31 | 50.1 | >100 | >2 |
| 32 | 10 | >100 | >10 |

| | | | |
|----|------|------|------|
| 33 | 79.4 | >100 | >1 |
| 34 | 100 | >100 | >1 |
| 35 | 1.8 | >320 | >178 |
| 36 | 5.6 | >320 | >57 |
| 37 | 4.0 | >100 | >25 |
| 38 | >320 | >320 | |
| 39 | >320 | >320 | |
| 40 | >100 | >100 | |
| 41 | 56 | 56 | 1 |
| 42 | 22.4 | 100 | >4 |
| 43 | 10 | 18 | >1 |
| 44 | 1.0 | >320 | >320 |
| 45 | >100 | >100 | |
| 46 | 3.2 | 45 | 14 |
| 49 | 2.4 | 19.1 | 8 |
| 51 | 32 | 32 | |
| 52 | 1.7 | 5.6 | 3 |
| 53 | 5.3 | >320 | >60 |
| 56 | 1.6 | >320 | >203 |
| 59 | >320 | >320 | |
| 60 | 158 | >320 | >2 |
| 61 | 0.89 | 56 | 63 |
| 62 | 1.6 | >100 | >63 |
| 65 | 158 | >320 | >2 |
| 66 | 1.4 | 6.3 | 5 |
| 67 | 5.2 | >320 | >62 |

| | | | |
|----|------|------|------|
| 68 | 16 | >320 | >20 |
| 70 | 1.2 | >320 | >267 |
| 71 | 14.1 | >320 | 23 |
| 73 | ND | | |
| 74 | 10 | 250 | 25 |
| 75 | 5.0 | >100 | >20 |
| 76 | >320 | >320 | |
| 77 | >320 | >320 | |
| 78 | 10 | 79.4 | 8 |
| 79 | 45 | >320 | >7 |
| 80 | 50 | >320 | >6 |
| 81 | 8.0 | 112 | 14 |
| 82 | 3.0 | >320 | >107 |
| 83 | 100 | >320 | >3 |
| 84 | 16 | >320 | >20 |
| 85 | 16 | >320 | >20 |
| 86 | 17 | >320 | >19 |
| 87 | 10.6 | >320 | >30 |
| 88 | 8.8 | >160 | >18 |
| 89 | 1.8 | 29 | 16 |
| 90 | 5.2 | >320 | >61 |
| 91 | 56 | >320 | >6 |
| 92 | 5.6 | 56 | 10 |
| 93 | >320 | >320 | |
| 94 | 46.8 | >320 | >7 |
| 95 | >320 | >320 | |

| | | | |
|-----|------|------|-------|
| 96 | 19.1 | 100 | 5 |
| 97 | >320 | >320 | |
| 98 | 100 | >320 | >3.2 |
| 99 | 141 | >320 | >2 |
| 100 | 11.1 | >320 | >29 |
| 101 | 2.0 | >320 | >160 |
| 102 | 5.6 | >320 | >57 |
| 103 | 1.7 | >320 | >188 |
| 104 | 5.2 | >320 | >61 |
| 105 | 14 | >320 | >23 |
| 106 | 0.27 | >320 | >1185 |
| 107 | 13.5 | >320 | >23 |
| 108 | 6.0 | >320 | >53 |
| 109 | 20 | >320 | >16 |
| 110 | 1.3 | >320 | >246 |
| 111 | 29.5 | >320 | >11 |
| 112 | 27 | >320 | >12 |
| 113 | 10 | >320 | >32 |
| 114 | 0.55 | >320 | >582 |
| 115 | 19 | >320 | >17 |
| 116 | 0.6 | >320 | >533 |
| 117 | 1.0 | >320 | >320 |
| 118 | 17.8 | >320 | >18 |
| 119 | 1.1 | >320 | >291 |
| 120 | 0.46 | >320 | >695 |
| 121 | >320 | >320 | |

| | | | |
|-----|-------|------|------|
| 122 | 1.78 | 10 | 5 |
| 123 | >320 | >320 | |
| 124 | 126 | >320 | >2 |
| 125 | >100 | 100 | |
| 126 | >320 | >320 | |
| 127 | >100 | ND | |
| 128 | >320 | >320 | |
| 129 | >320 | >320 | |
| 130 | 15.8 | >100 | >6 |
| 131 | >100 | >100 | |
| 132 | 5.6 | >320 | >57 |
| 133 | >177 | 177 | |
| 134 | 56.2 | >320 | >5 |
| 135 | 1.9 | >320 | >168 |
| 136 | >320 | >320 | |
| 137 | 223.9 | >320 | >1 |
| 138 | >41.7 | 41.7 | |
| 139 | 3.5 | >320 | >91 |
| 140 | 39 | >320 | >8 |
| 141 | 5.4 | >320 | >59 |
| 142 | 8.9 | >320 | >36 |
| 143 | 10 | >320 | >32 |
| 144 | 103.5 | >320 | >3 |
| 145 | >320 | >320 | |
| 146 | 0.38 | >320 | >842 |
| 147 | 205 | >320 | >1 |

| | | | |
|-----|-------|-------|-------|
| 148 | 0.25 | >320 | >1280 |
| 149 | 1.78 | >320 | >180 |
| 150 | >320 | >320 | |
| 151 | 0.32 | 177.8 | 555 |
| 152 | 1.78 | >320 | >180 |
| 153 | 0.12 | >320 | >2667 |
| 154 | 5.5 | >320 | >58 |
| 155 | 0.18 | >320 | >1778 |
| 156 | 35.5 | >320 | >9 |
| 157 | 0.56 | >320 | >571 |
| 158 | 5.9 | >320 | >54 |
| 159 | 2.4 | >320 | >133 |
| 160 | 5.0 | >320 | >64 |
| 161 | 0.17 | >100 | >588 |
| 162 | 0.32 | >100 | >312 |
| 163 | 0.5 | >100 | >200 |
| 164 | 0.71 | >100 | >141 |
| 165 | 0.20 | >100 | >500 |
| 166 | 5.6 | >100 | >18 |
| 167 | 0.083 | >100 | >1204 |
| 168 | 0.32 | >100 | >312 |
| 169 | 18 | >100 | >5 |
| 170 | 0.20 | >100 | >500 |
| 171 | 0.71 | >100 | >140 |
| 172 | 0.79 | >100 | >126 |
| 173 | 0.08 | >100 | >1250 |

| | | | |
|-----------|-------|------|-------|
| 174 | 0.056 | >100 | >1786 |
| 175 | 0.18 | >100 | >555 |
| 176 | 0.14 | >100 | >714 |
| 177 | 0.5 | >100 | >200 |
| 178 | 0.10 | >100 | >1000 |
| 179 | 1.78 | >100 | >56 |
| 180 | 0.056 | >100 | >1785 |
| 181 | 0.1 | >100 | >1000 |
| 182 | 0.18 | >100 | >556 |
| 183 | 0.03 | >100 | >3333 |
| 184 | 0.19 | >100 | >526 |
| 185 | 0.50 | >100 | >200 |
| 186 | ND | ND | |
| 187 | ND | ND | |
| 188 | ND | ND | |
| | | | |
| WIN 51711 | 0.78 | >60 | >77 |
| WIN 52084 | 0.07 | >10 | >143 |
| WIN 54954 | 2.13 | >63 | >30 |
| Pirodavis | 0.03 | >10 | >300 |

Normal Human Bronchial Epithelial Cell Assay

Normal human bronchial cells were obtained from cadavers and cultured. The cells were plated at 2×10^4 per well in a 96 well plate. They were allowed to adhere and grow for 24 hours in 200 μ L of serum-free bronchial/tracheal epithelial cell growth medium at

37 °C with 5% CO₂. Human Rhinovirus-serotype 10 (HRV-10) was purchased from American Type Culture Collection (ATCC). To start the assay, the supernatant was removed, and HRV-10 at an m.o.i. of 10 (virus particles/cell) was added to each well along with the appropriate amount of compound of formula I or II. The plate was then incubated at 34 °C. After 3 hours the supernatant was removed, and 200 µL of media was added along with the same concentration of compound as used in the beginning of the assay. The plates were incubated for 3-4 days at 34 °C. To determine the amount of cell growth, an MTT assay (0.5 mgs/mL), as described in Mosmann, T.J. *J. Immunol. Methods* 1983, 65, 55-63, which is incorporated herein by reference, was performed on the cells, and the plate was read at an optical density of 540 nm. The results of the assay are set forth in Table 3. The compounds were tested against control compound Pirodavis, obtained from Janssen Pharmaceuticals. The EC₅₀ was measured as described above for the HI-HeLa Cell Culture Assay.

TABLE 3

| <u>Compound #</u> | <u>ED₅₀(µM)</u> |
|-------------------|----------------------------|
| 3 | 0.04 |
| 4 | 0.15 |
| 5 | 0.001 |
| 11 | 0.0007 |
| 12 | 0.004 |
| 13 | 0.0004 |
| 27 | 0.07 |
| 85 | 0.005 |
| pirodavis | 0.0075 |

Anticocksackieviral HI-HeLa Cell Culture Assay

The ability of compounds to protect cells against CVB-3 infection was measured by the XTT dye reduction method, which is described in Weislow, O.S., R.Kiser, D.L. Fine, J.Bader, R.H. Shoemaker, and M.R. Boyd, 1989, J. Natl. Cancer Inst. 81:577-586, which is incorporated herein by reference. Specifically, HI-HeLa cells were infected with CVB-3 at a multiplicity of infection (m.o.i.) of 0.08 or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8×10^5 cells per mL and incubated with appropriate concentrations of compound. One day later, XTT/PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound free, mock-infected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of drug that decreased the percentage of formazan produced in compound treated, mock-infected cells to 50% of that produced in compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50} .

The Cocksackie strain B-3 (CVB-3) was purchased from American Type Culture Collection (ATCC). Virus stocks were propagated and antiviral assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium with 10% fetal bovine serum.

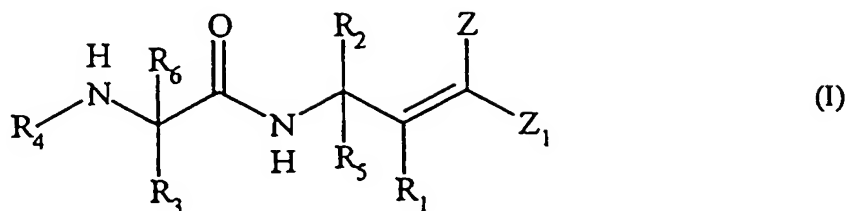
The compounds were tested against control compound WIN 54954, obtained from Sterling Winthrop Pharmaceuticals, and control compound Pirodavis, obtained from Janssen Pharmaceuticals.

TABLE 4

| <u>Compound #</u> | <u>EC₅₀ (μM)</u> | <u>CC₅₀ (μM)</u> | <u>TI</u> |
|-------------------|-----------------------------|-----------------------------|-----------|
| 3 | 39.8 | >320 | >8 |
| 11 | 8.9 | >320 | >35 |
| 13 | >100 | >100 | |
| 21 | 158 | >320 | >2 |
| 23 | >100 | >100 | |
| 24 | 10 | 10 | 1 |
| 27 | 20 | 102.7 | >5 |
| 37 | 17.8 | >100 | >5.6 |
| 41 | >100 | >100 | |
| WIN 54954 | >100 | >100 | |
| Pirodavis | >100 | >100 | |

We claim:

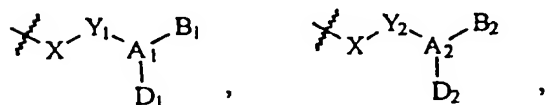
1. A compound of the formula (I):



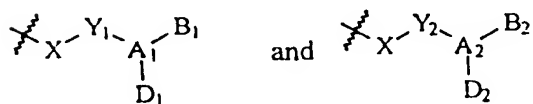
wherein

R₁ is H, F, an alkyl group, OH, SH, an O-alkyl group, or an S-alkyl group;

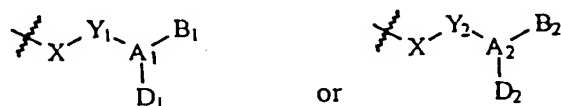
R₂ and R₃ are independently selected from H,



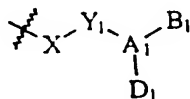
or an alkyl group, wherein said alkyl group is different from



with the proviso that at least one of R₂ or R₃ must be



and wherein, when R₂ or R₃ is



X is =CH or =CF and Y₁ is =CH or =CF

or X and Y₁ together with Q' form a three-membered ring

in which Q' is -C(R₁₀)(R₁₁)- or -O-, X is -CH- or -CF-, and Y₁ is -CH-, -CF-, or -C(alkyl)-, where R₁₀ and R₁₁ independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is -CH₂-, -CF₂-, -CHF-, or -S-,

and

Y₁ is -O-, -S-, -NR₁₂-, -C(R₁₃)(R₁₄)-, -C(O)-, -C(S)-, or -C(CR₁₃R₁₄)-

wherein R₁₂ is H or alkyl, and R₁₃ and R₁₄ independently are H, F, or an alkyl group, or, together with the atom to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

and A₁ is C, CH, CF, S, P, Se, N, NR₁₅, S(O), Se(O), P-OR₁₅, or P-NR₁₅R₁₆

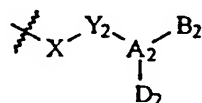
wherein R₁₅ and R₁₆ independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

and D₁ is a moiety with a lone pair of electrons capable of forming a hydrogen bond;

and B₁ is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, -OR₁₇, -SR₁₇, -NR₁₇R₁₈, -NR₁₉NR₁₇R₁₈, or -NR₁₇OR₁₈

wherein R₁₇, R₁₈, and R₁₉ independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an

acyl group, or, wherein any two of R_{17} , R_{18} , and R_{19} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group; and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group; and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N; and wherein, when R_2 or R_3 is



X is $=CH$ or $=CF$ and Y_2 is $=C$, $=CH$ or $=CF$,

or X and Y_2 together with Q' form a three-membered ring

in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_2 is $-CH-$, $-CF-$, or $-C(\text{alkyl})-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$,

and

Y_2 is $-O-$, $-S-$, $-N(R'_{12})-$, $-C(R'_{13})(R'_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR'_{13}R'_{14})-$

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR'_{13}$, $-NR'_{13}R'_{14}$, $-C(O)-R'_{13}$, $-SO_2R'_{13}$, or $-C(S)R'_{13}$, and R'_{13} and R'_{14} , independently are H, F, or an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

and wherein any combination of Y_2 , A_2 , B_2 , and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and A_2 is C, CH, CF, S, P, Se, N, NR_{15} , $S(O)$, $Se(O)$, $P-OR_{15}$, or $P-NR_{15}R_{16}$

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

and D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond;

and B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$

wherein R_{17} , R_{18} , and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or, wherein any two of R_{17} , R_{18} , and R_{19} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

R_3 and R_6 are independently H, F, or an alkyl group;

R_4 is H, OH, or a suitable organic moiety;

Z and Z₁ are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, -C(O)R₂₁, -CO₂R₂₁, -CN, -C(O)NR₂₁R₂₂, -C(O)NR₂₁OR₂₂, -C(S)R₂₁, -C(S)NR₂₁R₂₂, -NO₂, -SOR₂₁, -SO₂R₂₁, -SO₂NR₂₁R₂₂, -SO(NR₂₁)(OR₂₂), -SONR₂₁, -SO₃R₂₁, -PO(OR₂₁)₂, -PO(R₂₁)(R₂₂), -PO(NR₂₁R₂₂)(OR₂₃), -PO(NR₂₁R₂₂)(NR₂₃R₂₄), -C(O)NR₂₁NR₂₂R₂₃, or -C(S)NR₂₁NR₂₂R₂₃,

wherein R₂₁, R₂₂, R₂₃, and R₂₄ are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or acyl group, or a thioacyl group, or wherein any two of R₂₁, R₂₂, R₂₃, and R₂₄, together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

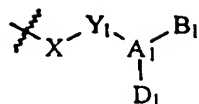
or Z₁, as defined above, together with R₁, as defined above, and the atoms to which Z₁ and R₁ are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z₁, both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or a pharmaceutically acceptable prodrug, salt, or solvate thereof;

and wherein said compound, pharmaceutically acceptable prodrug, salt, or solvate thereof, has antipicornaviral activity with an EC₅₀ less than or equal to 100 μM in the HI-HeLa cell culture assay.

2. A compound of claim 1 wherein R₁ is H or F, or a pharmaceutically acceptable prodrug, salt, or solvate thereof.
3. A compound of claim 1 wherein R₄ is an acyl group or a sulfonyl group, or a pharmaceutically acceptable prodrug, salt, or solvate thereof.
4. A compound of claim 1, wherein at least one of R₂ or R₃ is



or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

5. A compound according to claim 4, wherein D_1 is $-\text{OR}_{25}$, $=\text{O}$, $=\text{S}$, $\equiv\text{N}$, $=\text{NR}_{25}$, or $-\text{NR}_{25}\text{R}_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

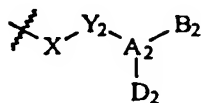
6. A compound according to claim 5 wherein D_1 is $=\text{O}$; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

7. A compound according to claim 4, wherein A_1 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

8. A compound according to claim 7 wherein A_1 is C; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

9. A compound according to claim 4 wherein B_1 is $\text{NR}_{17}\text{R}_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein R_{17} and R_{18} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

10. A compound according to claim 1, wherein at least one of R_2 or R_3 is



or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

11. A compound according to claim 10, wherein D_2 is $-\text{OR}_{25}$, $=\text{O}$, $=\text{S}$, $\equiv\text{N}$, $=\text{NR}_{25}$, or $-\text{NR}_{25}\text{R}_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

12. A compound according to claim 11, wherein D_2 is $=\text{O}$; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

13. A compound according to claim 10, wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

14. A compound according to claim 13, wherein A_2 is C; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

15. A compound according to claim 10 wherein B_2 is $\text{NR}_{17}\text{R}_{18}$,

wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or

wherein R_{17} and R_{18} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

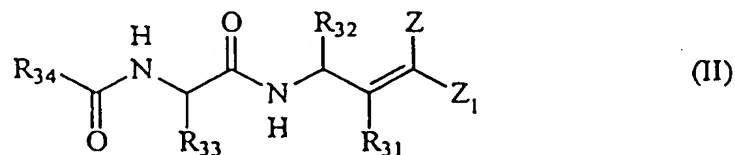
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

16. A compound according to claim 1, wherein A_1 is C, CH, S, or S(O) and wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

17. A compound according to claim 1 wherein Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$;

wherein R_{21} , R_{22} , and R_{23} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21} , R_{22} , and R_{23} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group, or Z and Z_1 , together with the atoms to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

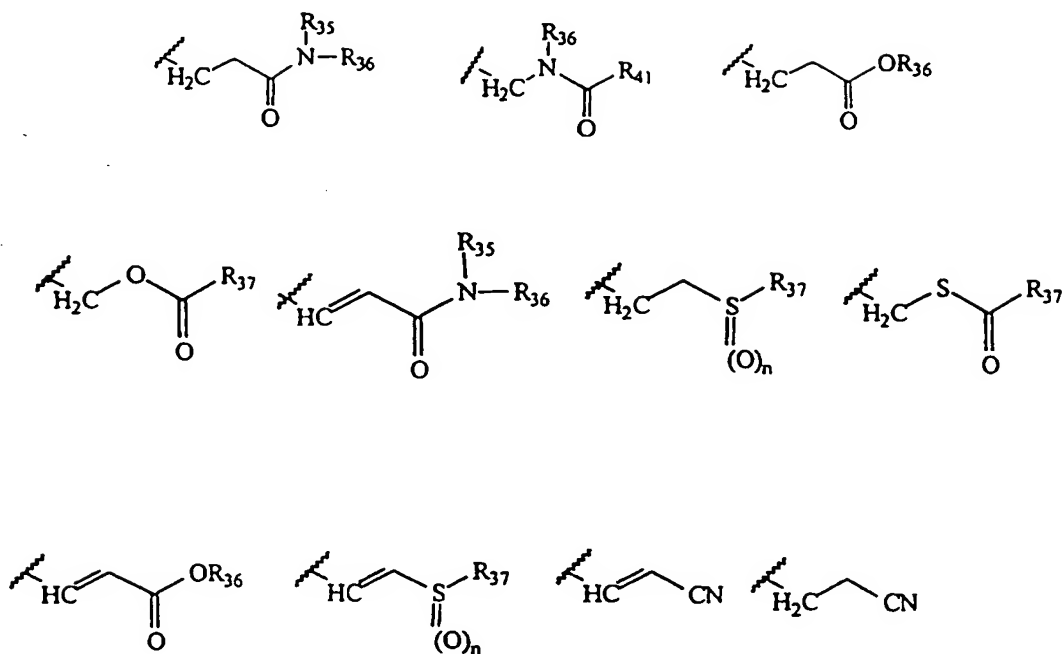
18. A compound according to claim 1, wherein said compound has the formula II:



wherein

R_{31} is H, F or an alkyl group;

R₃₂ is selected from one of the following moieties:



wherein

R₃₅ is H, an alkyl group, an aryl group, -OR₃₈, or -NR₃₈R₃₉, and

R₃₆ is H or an alkyl group,

or R₃₅ and R₃₆, together with the atom(s) to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R₄₁ is H, an alkyl group, an aryl group, -OR₃₈, -SR₃₉, -NR₃₈R₃₉, -NR₄₀NR₃₈R₃₉, or

-NR₃₈OR₃₉, or R₄₁ and R₃₆, together with the atom to which they are attached, form a heterocycloalkyl group, and

R₃₇ is an alkyl group, an aryl group, or -NR₃₈R₃₉;

wherein R₃₈, R₃₉, and R₄₀ independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an

acyl group, or, wherein any two of R_{38} , R_{39} , and R_{40} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

n is 0, 1 or 2;

R_{33} is H or an alkyl group;

R_{34} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

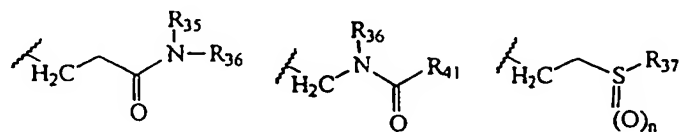
wherein R_{21} , R_{22} , R_{23} , and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21} , R_{22} , R_{23} , and R_{24} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or Z and Z_1 , together with the atoms to which they are bonded, form a heterocycloalkyl group;

or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

19. A compound according to claim 18 wherein Z and Z₁ are independently H, an aryl group, or a heteroaryl group, -C(O)R₂₁, -CO₂R₂₁, -CN, -C(O)NR₂₁R₂₂, -C(O)NR₂₁OR₂₂, -C(S)R₂₁, -C(S)NR₂₁R₂₂, -NO₂, -SOR₂₁, -SO₂R₂₁, -SO₂NR₂₁R₂₂, -SO(NR₂₁)(OR₂₂), -SONR₂₁, -SO₃R₂₁, -C(O)NR₂₁NR₂₂R₂₃, or -C(S)NR₂₁NR₂₂R₂₃; wherein R₂₁, R₂₂, and R₂₃ are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein any two of R₂₁, R₂₂, and R₂₃, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, or Z and Z₁, together with the atoms to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

20. A compound according to claim 18 wherein R₃₂ is selected from one of the following moieties:



wherein

R₃₅ is H, an alkyl group, an aryl group, -OR₃₈, -SR₃₉, -NR₃₈R₃₉, -NR₄₀NR₃₈R₃₉, or -NR₃₈OR₃₉, and

R₃₆ is H or an alkyl group,

or R₃₅ and R₃₆, together with the atom to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

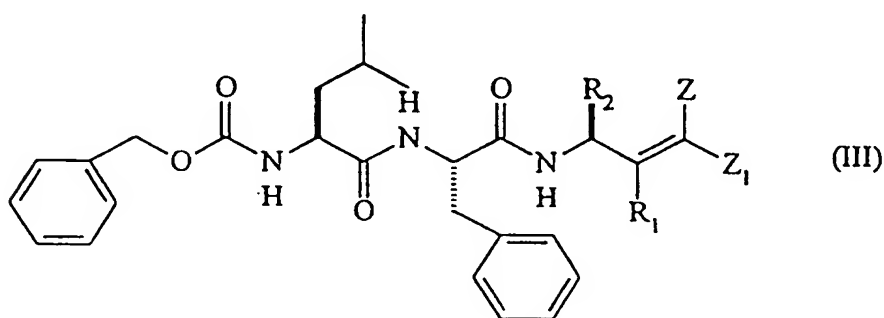
R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$;

wherein R_{38} , R_{39} , and R_{40} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or, wherein any two of R_{38} , R_{39} , and R_{40} , together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

n is 0, 1 or 2;

or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

21. A compound according to claim 1, wherein said compound has the formula III:



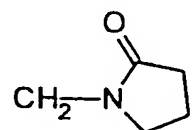
wherein

R_2 is $CH_2CH_2C(O)NHCPH_3$, R_1 is H, Z is H, and Z_1 is $CO_2CH_2CH_3$,

R_2 is $CH_2CH_2C(O)NH_2$, R_1 is H, Z is H, and Z_1 is $CO_2CH_2CH_3$,

R_2 is $CH_2NHC(O)CH_3$, R_1 is H, Z is H, and Z_1 is $CO_2CH_2CH_3$,

R_1 is H, Z is H, and Z_1 is $CO_2CH_2CH_3$, and R_2 is



R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is CO_2CH_3 , and Z_1 is H,

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is CO_2CH_3 ,

R_2 is $\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$,

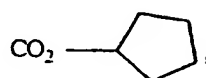
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{CH}_3$,

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is CN,

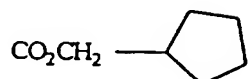
R_2 is $\text{CH}_2\text{NHC}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$,

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}(\text{CH}_3)_2$,

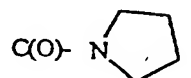
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



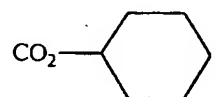
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



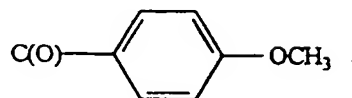
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$,

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{C}(\text{O})\text{Ph}$,

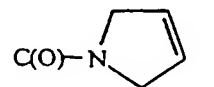
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



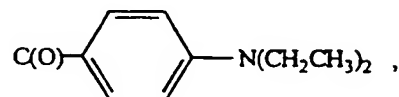
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is

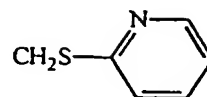


R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is CH_2Cl , or

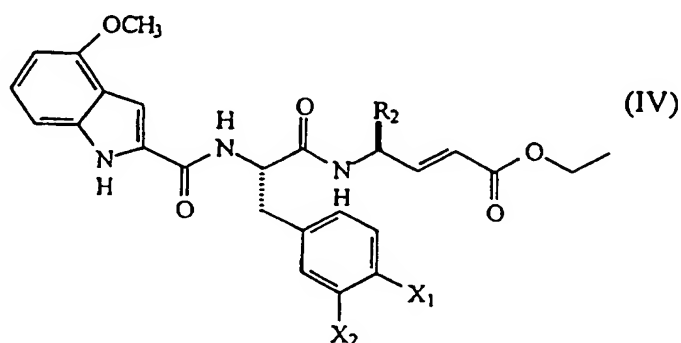
R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is



or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

22. A compound according to claim 1, wherein said compound has the formula

IV:

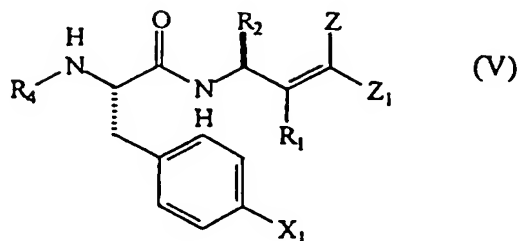


wherein

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, X_1 is H, F, or Cl, and X_2 is H, F, or Cl; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

23. A compound according to claim 22 wherein X_1 is Cl and X_2 is H; X_1 is F and X_2 is H; or X_1 is H and X_2 is F; or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

24. A compound according to claim 1, wherein said compound has the formula V:



wherein:

R_4 is $\text{PhCH}_2\text{OC(O)}$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; or

R_4 is $\text{CH}_3\text{CH}_2\text{CH}_2\text{SO}_2$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; or

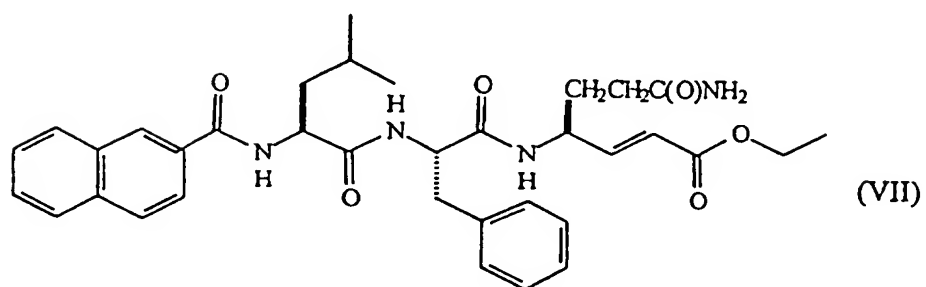
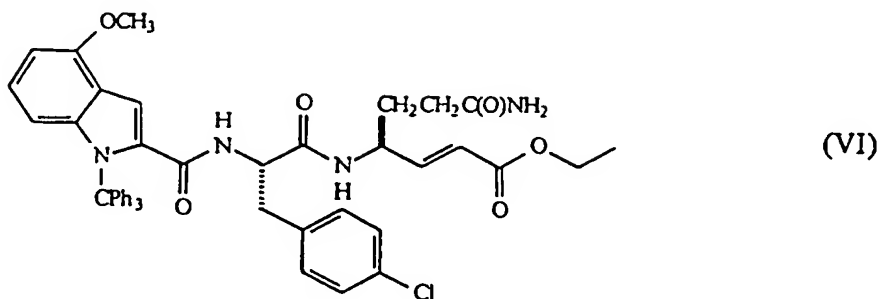
R_4 is PhCH_2SO_2 , X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; or

R_4 is $\text{CH}_3\text{CH}_2\text{SO}_2$, X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$; or

R_4 is PhSO_2 , X_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_1 is H, Z is H, and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$;

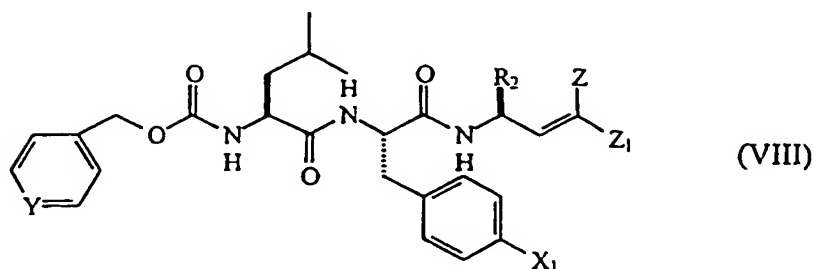
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

25. A compound according to claim 1, wherein said compound has the formula VI or VII:



or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

26. A compound according to claim 1, wherein said compound has the formula VIII:



wherein

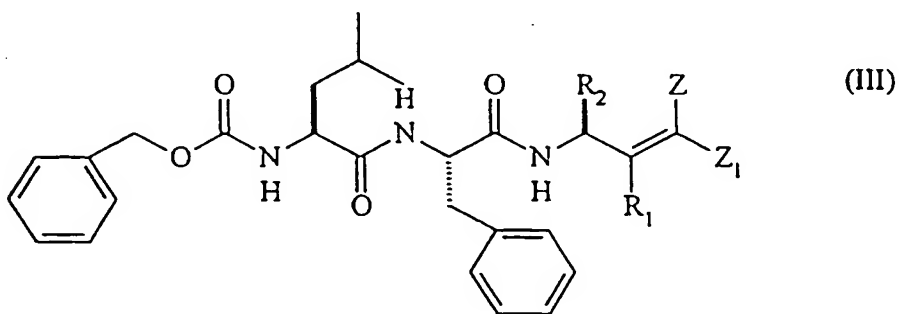
X₁ is F, R₂ is CH₂CH₂C(O)NH₂, Y is CH, Z is H, and Z₁ is CO₂CH₂CH₃; or

X₁ is H, R₂ is CH₂CH₂C(O)NH₂, Y is N, Z is H, and Z₁ is CO₂CH₂CH₃; or

X₁ is H, R₂ is CH₂CH₂C(O)NH₂, Y is CH, Z is H, and Z₁ is C(O)N(CH₃)OCH₃;

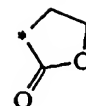
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

27. A compound according to claim 1, wherein said compound has the formula III:

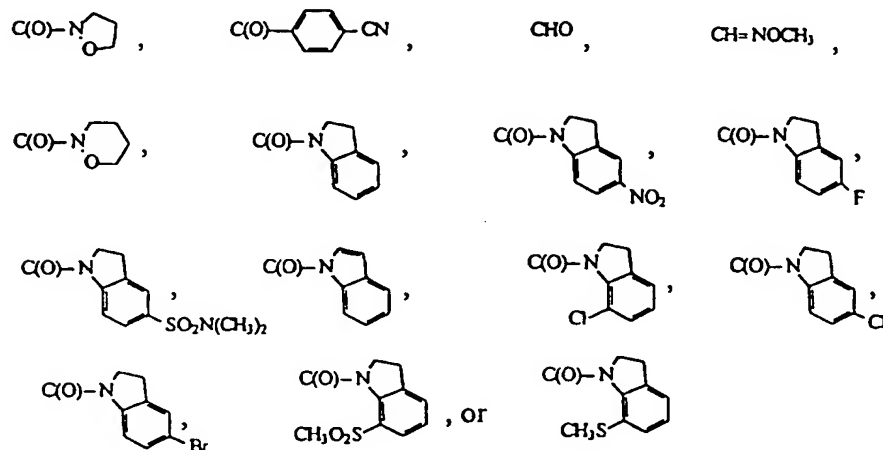


wherein R₂ is CH₂CH₂C(O)NH₂, R₁ is H, Z is CH₃ and Z₁ is CO₂CH₂CH₃.

R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, and Z and Z_1 together form



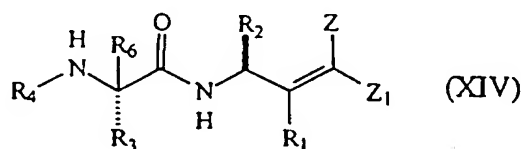
or wherein R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, Z is H, and Z_1 is selected from:



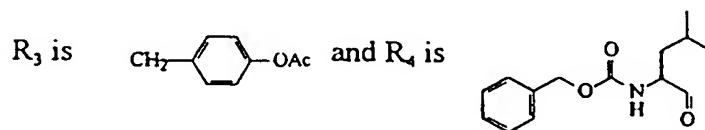
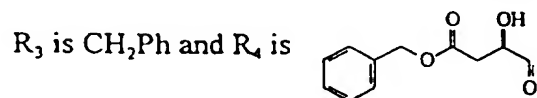
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

28. A compound according to claim 1, wherein said compound has the formula

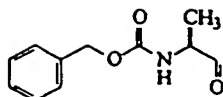
XIV:



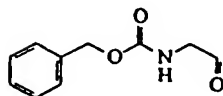
wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and




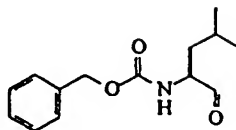
R_3 is CH_2Ph and R_4 is



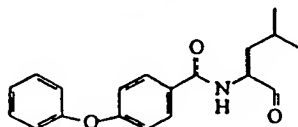
R_3 is CH_2Ph and R_4 is

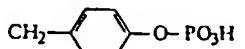


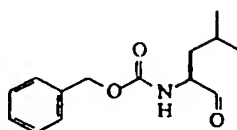
R_3 is CH_2 -- OCH_3 and R_4 is



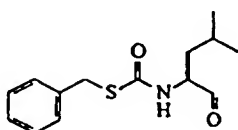
R_3 is CH_2Ph and R_4 is



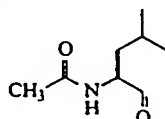
R_3 is CH_2 -- $\text{O-PO}_3\text{H}$ and R_4 is



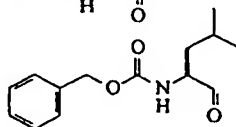
R_3 is CH_2Ph and R_4 is



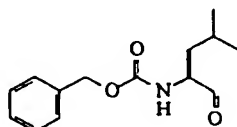
R_3 is CH_2Ph and R_4 is



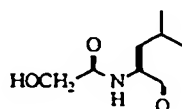
R_3 is CH_2CH_3 and R_4 is

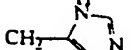


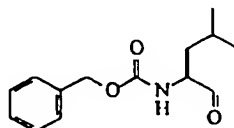
R_3 is CH_3 and R_4 is

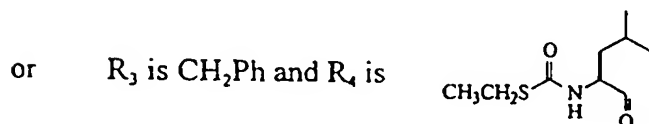
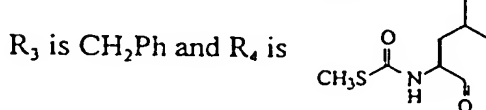
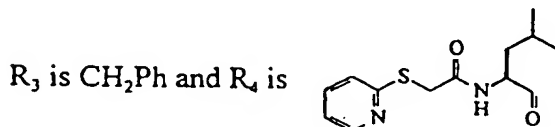
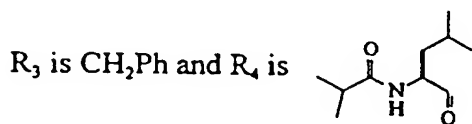
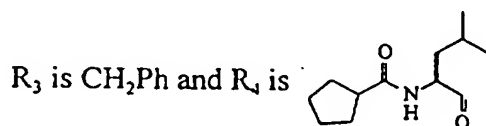
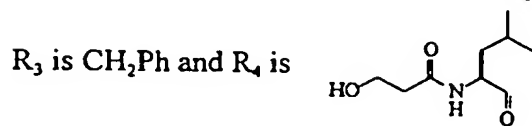
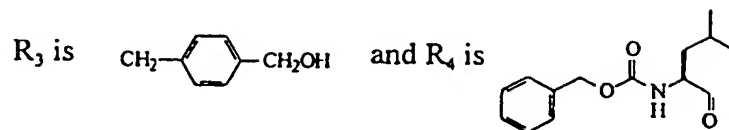
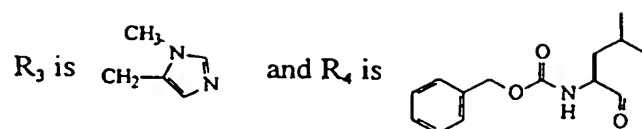


R_3 is CH_2Ph and R_4 is



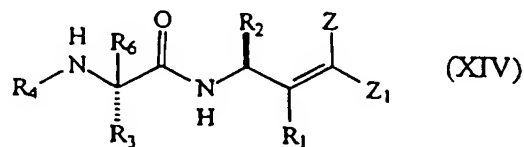
R_3 is CH_2 -- and R_4 is





or a pharmaceutically acceptable prodrug, salt or solvate thereof.

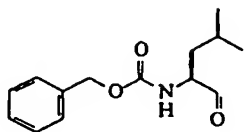
29. A compound according to claim 1, wherein said compound has the formula XIV:



wherein R_6 is H, R_1 is H, R_3 is CH_2Ph , R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, Z and Z_1 together form

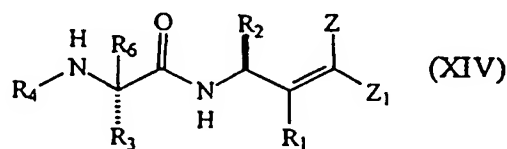


and R_4 is

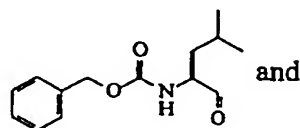


or a pharmaceutically acceptable prodrug, salt or solvate thereof.

30. A compound according to claim 1, wherein said compound has the formula XIV:



wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C(O)NH}_2$, R_4 is



and

R_3 is $\text{CH}_2-\text{C}_6\text{H}_4-\text{CN}$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

R_3 is CH(OH)CH_3 , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

R_3 is $\text{CH}_2-\text{C}_6\text{H}_{10}$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

R_3 is CH_2Ph , Z is H and Z_1 is C(O)N(OH)CH_3

R_3 is $\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{OH}$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

R_3 is $\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2\text{OCH}_3$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

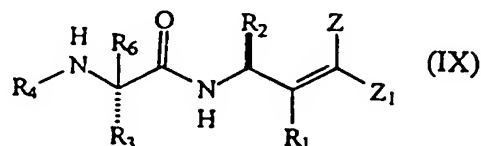
R_3 is $\text{CH}_2\text{CH(CH}_3)_2$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

R_3 is CH_2SCH_3 , Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

or R_3 is $\text{CH}_2\text{SCH}_2\text{CH}_3$, Z is H and Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$

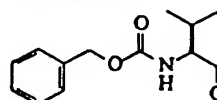
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

31. A compound according to claim 1, wherein said compound has the formula IX:

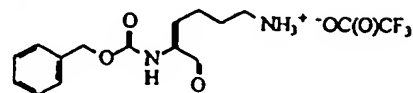


wherein R_6 is H, R_1 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, Z is H, and

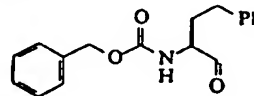
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



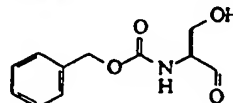
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



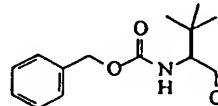
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



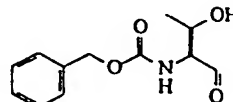
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



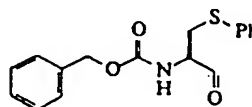
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



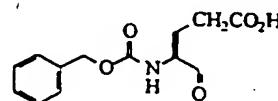
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



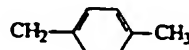
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



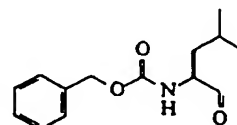
Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is



or Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is

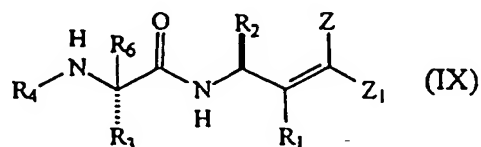


and R_4 is



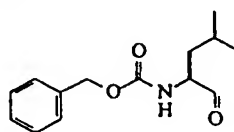
or a pharmaceutically acceptable prodrug, salt or solvate thereof.

32. A compound according to claim 1, wherein said compound has the formula IX:

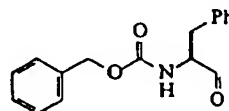


wherein R_6 is H, R_3 is CH_2Ph , R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and

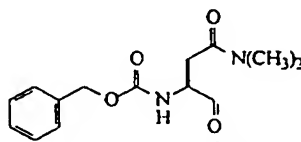
R_1 is OH, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



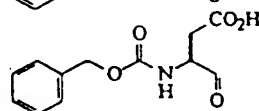
R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



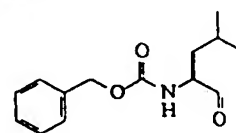
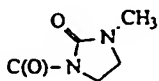
R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



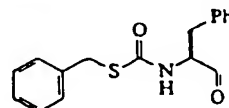
R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



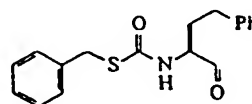
R_1 is H, Z is H, Z_1 is $\text{C}(\text{O})-\text{N}(\text{CH}_3)-$ and R_4 is

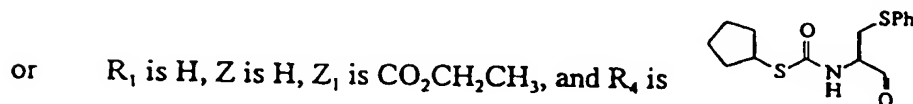
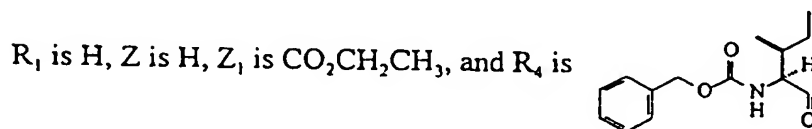
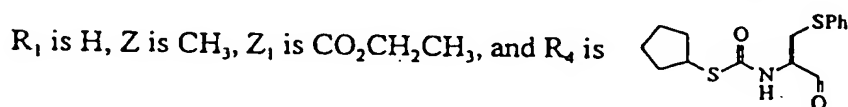
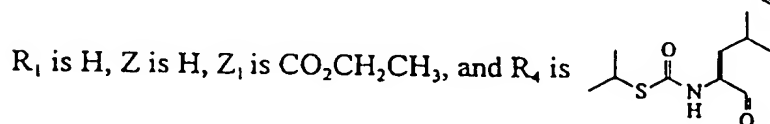
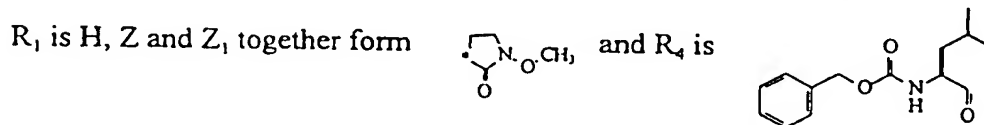
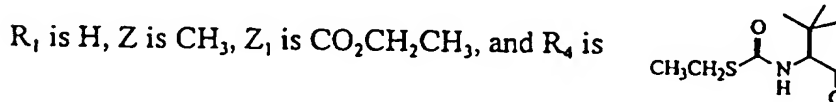
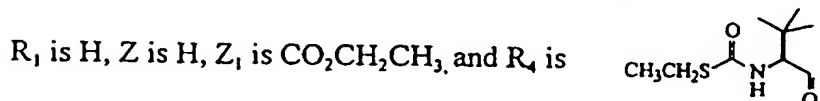
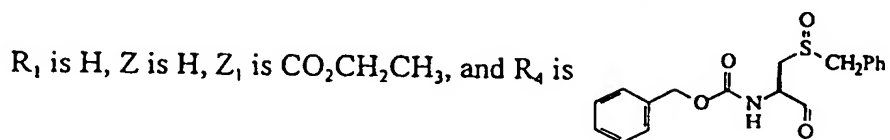
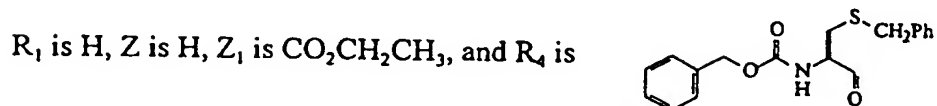
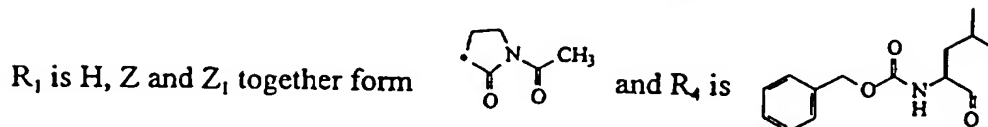
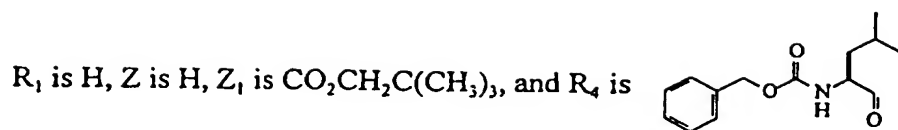


R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is



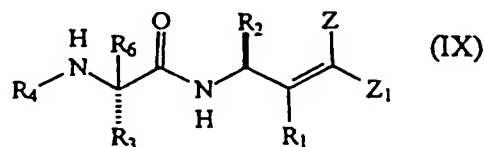
R_1 is H, Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, and R_4 is





or a pharmaceutically acceptable prodrug, salt or solvate thereof.

33. A compound according to claim 1, wherein said compound has the formula IX:



wherein R_6 is H, R_2 is $\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, R_1 is H, and

Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2 -, and R_4 is -

Z is CH_3 , Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2 -, and R_4 is -

Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2 -, and R_4 is -

Z is CH_3 , Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2 -, and R_4 is -


Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is -

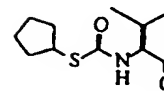
Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is -

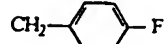
Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is -

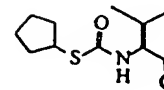
Z and Z_1 together form , R_3 is CH_2 -, and R_4 is -

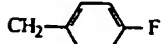
Z is H, Z_1 is $\text{CO}_2\text{CH}_2\text{CH}_3$, R_3 is CH_2Ph , and R_4 is -

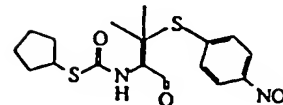
Z is H, Z₁ is CO₂CH₂CH₃, R₃ is  and R₄ is



Z is H, Z₁ is CO₂CH₂CH₃, R₃ is  and R₄ is



or Z is H, Z₁ is CO₂CH₂CH₃, R₃ is  and R₄ is



or a pharmaceutically acceptable prodrug, salt or solvate thereof.

34. A pharmaceutical composition comprising:

- (a) a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, or solvate thereof; and
- (b) a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

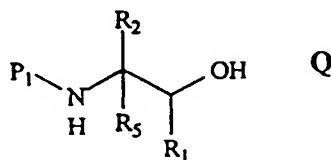
35. A method of treating a mammalian disease condition mediated by picornaviral protease activity that comprises administering to a mammal for the purpose of said treating a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

36. A method of inhibiting the activity of a picornaviral 3C protease that comprises contacting the picornaviral 3C protease for the purpose of said inhibiting with an effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

37. A method of inhibiting the activity of a rhinoviral protease that comprises contacting the rhinoviral protease for the purpose of said inhibiting with an effective

amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

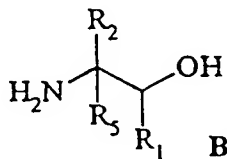
38. A method of making a compound according to claim 1, comprising converting a compound of formula Q



wherein R_1 , R_2 and R_5 are as defined in claim 1, and P_1 is a protective group, or a salt or solvate thereof, to a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

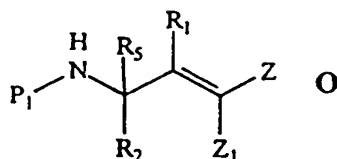
39. A method according to claim 38, wherein P_1 is benzyloxy carbonyl or t-butoxycarbonyl.

40. A method a making a compound according to claim 1, comprising converting a compound of the formula B:



wherein R_1 , R_2 and R_5 are as defined in claim 1, or a salt or solvate thereof, to a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

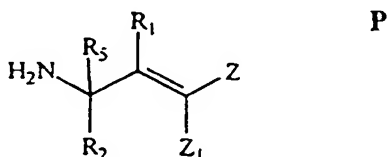
41. A method of making a compound according to claim 1, comprising converting a compound of formula O,



wherein R_1 , R_2 , R_5 , Z and Z_1 are as defined in claim 1 and P_1 is a protective group, or a salt or solvate thereof, to a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

42. A method according to claim 41, wherein P_1 is benzyloxy carbonyl or t-butoxycarbonyl.

43. A method of preparing a compound according to claim 1, comprising converting a compound of formula P:



wherein R_1 , R_2 , R_5 , Z and Z_1 are as defined in claim 1, or a salt or solvate thereof, to a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable prodrug, salt or solvate thereof.

44. A compound according to claim 1, or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt, solvate, or any crystal form thereof, wherein said antipicornaviral activity is antirhinoviral activity.

45. A compound according to claim 1, or a pharmaceutically acceptable prodrug

or a pharmaceutically acceptable salt, solvate, or any crystal form thereof, wherein said antipicornaviral activity is antioxsackieviral activity.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/08112

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/06 C07C237/22 C07D521/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|------------|--|----------------------|
| A | VAILLANCOURT, MARC ET AL: "Synthesis of novel inhibitors of the HIV-1 protease: Difunctional enols of simple N-protected amino acids" BIOORG. MED. CHEM. , vol. 2, 1994, pages 343-355, XP002043058 see the whole document | 1-45 |
| A | VAILLANCOURT, MARC ET AL: "Difunctional enols of N-protected amino acids as low molecular weight and novel inhibitors of HIV-1 protease" BIOORG. MED. CHEM. LETT. , vol. 3, no. 6, 1993, pages 1169-1174, XP002043059 see the whole document | 1-45 |

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

9 October 1997

Date of mailing of the international search report

22.10.97

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